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The Role of Environmental Tobacco Smoke in Asthma Induction and Exacerbation in Children and Adults

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ABBREVIATIONS

AA	African-American
ABS	Australian Bureau of Statistics
AQOL	Asthma-related (or asthma-specific) quality of life
Asymm	Asymmetry, associated with Egger's test of publication bias
ATS	American Thoracic Society
BAMSE	B=children, A=allergy, M=environment, S=Stockholm, E=epidemiology
BHR	Bronchial hyperreactivity
BR	Bronchial reactivity
BTS	British Thoracic Society
CC	Case-control study
CCR	Cotinine/creatinine ratio
CI	Confidence interval
CO	Carbon monoxide
COHb	Carboxyhaemoglobin
COLD (or COPD)	Chronic obstructive lung (or pulmonary) disease
cpm	counts per minute
CS (or CrSec)	Cross-sectional study
d.f.	degrees of freedom
ECRHS	European Community Respiratory Health Study
EPA	Environmental Protection Agency
ER	Emergency room or department
ESP	Epidemiology standardization project
ETS	Environmental tobacco smoke
ETSC	ETS challenge
$FEF_{x\%}$	Forced expiratory flow at x% of forced vital capacity
FEV_1	Forced expiratory volume in 1 second
FRC	Functional residual capacity
FVC	Forced vital capacity
F&L	Method of Fry & Lee (2000)
GP	General practitioner
GPRD	General Practice Research Database

HDM	House dust mite
Het	Heterogeneity
HSSQCY	Health and Social Survey of Quebec Children and Youth
ICHPPC	International classification of health problems in primary care
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IRR	Incidence rate ratio
ISAAC	International study of asthma and allergies in childhood
IUATLD	International Union Against Tuberculosis and Lung Disease
LCL	Lower confidence limit (also RRl)
LS	Longitudinal study
MEF_{50}	Maximal expired flow rate at 50% of FVC
MLR	Multiple logistic regression
MMEFR	Mid-maximal expiratory flow rate
MRC	Medical Research Council
NA	Not applicable
NCDS	National Child Development Study
NHANES III	Third National Health and Nutrition Examination Survey
NHLI	National Heart and Lung Institute
NIH	National Institutes of Health (USA)
NK	Not known
NOS	Not otherwise specified
NS	Not significant
OR	Odds ratio
PAH	Polycyclic aromatic hydrocarbons
PC_{20} (or PD_{20})	Provocative concentration (or dose) of histamine or methacholine to produce a 20% increase in FEV_1
PC_{100}SRAW	Provocative concentration of histamine or methacholine to produce a 100% increase in specific airway resistance
PEACE	Pollution Effects on Asthmatic Children in Europe
PEFR	Peak expiratory flow rate
PIAMA	Prevention and Incidence of Asthma and Mite Allergy
PNLSC	P.N. Lee Statistics and Computing Ltd.
ppm	parts per million
PS (or Pr or Prosp)	Prospective study
REF	Six-character reference identifying studies in asthma induction databases (listed in Tables 8.1 and 9.1)
RR	Relative risk
RV	Residual volume
RVC	Relaxed vital capacity
SAPALDIA	Swiss Cohort Study on Air Pollution and Lung Diseases in Adults
SCARPOL	Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen
SD	Standard deviation
SE	Standard error
SES	Socio-economic status

SIDRIA	Studi Italiani sui Disturbi Respiratori nell'Infanzia e l'Ambiente (Italian Studies on Respiratory Disorders in Childhood and the Environment)
SIDS	Sudden infant death syndrome
SPT	Skin prick test
SRAW	Specific airway resistance
SS	Sidestream *or* Smoke sensitive
TLC	Total lung capacity
UCL	Upper confidence limit (also RRu)
UV	Ultra-violet
URI	Upper respiratory tract infection
VC	Vital capacity
$VMAX_{x\%}$	Maximum volume at x% of vital capacity
WHO	World Health Organization

Chapter 1

OBJECTIVES

The main objective of the work described in this book is to determine the role of environmental tobacco smoke (ETS) exposure in asthma induction and exacerbation in children and adults. A secondary objective is to consider whether views on the role of ETS in asthma that have been expressed by various health authorities are justified.

In order to clarify the objectives it is necessary to define various terms precisely.

INDUCTION AND EXACERBATION

Asthma is characterised by episodic symptoms and variable airflow obstruction that occur either spontaneously or in response to environmental exposures. Individuals may be asthmatic or non-asthmatic, the asthmatic state implying the propensity for an asthmatic attack. An agent may "induce" the asthmatic state, causing an individual previously classified as non-asthmatic to be reclassified as asthmatic. An agent may also "exacerbate" asthma, by causing an attack in a known asthmatic or by increasing the severity of symptoms of asthma. Evidence relating to asthma exacerbation is considered in chapters 3 to 6, while evidence relating to asthma induction is considered in chapters 7 to 9.

ETS EXPOSURE

ETS exposure, or passive smoking, is the inhalation of tobacco smoke other than by puffing on a cigarette, cigar or pipe. ETS consists in the main part of sidestream smoke, emitted from the burning cigarette between puffs, and exhaled mainstream smoke, emitted from the smoker following each puff. Smoking by the mother in pregnancy (*in utero* exposure to maternal smoking) is not ETS exposure as such, as it does not involve inhalation of smoke by the fetus. However its role is also considered in this book.

Chapter 2

GENERAL APPROACH AND LAYOUT OF THE BOOK

2.1. INTRODUCTION

The evidence is considered in detail in five separate chapters, chapters 3, 4 and 5 relating to asthma exacerbation and chapters 8 and 9 to asthma induction.

For all these five sections, attempts were made to collect all relevant literature published up to and including 2004. Relevant literature was obtained from the extensive files on smoking and health accumulated by P.N. Lee Statistics and Computing Ltd. (PNLSC), from Medline searches, from the references of papers obtained, and from the references of other published reviews. Studies published only as abstracts were included. It was considered more important to obtain all the relevant evidence than to restrict attention unnecessarily to papers published in peer reviewed journals.

Within each section, papers that were found to contain relevant data were classified into separate studies, taking account that some papers described results from more than one study and that results from some studies were described in multiple publications.

Having all the relevant publications for each study, the processes carried out differed between studies of asthma exacerbation and asthma induction, due primarily to the much greater number of the induction studies (particularly in children) and their greater potential for formal meta-analysis.

2.2. ASTHMA EXACERBATION

Chapter 3 considers experimental chamber studies in which asthmatic subjects underwent a planned exposure to tobacco smoke. In many of these studies the exposure was from a smoking machine, and was not strictly ETS, being either sidestream smoke only or a mixture of mainstream and sidestream smoke, so not including a contribution from exhaled mainstream smoke. These studies were mainly of adults, but some were of children and some involved both adults and children. The studies were generally restricted to non-smokers, although the definition of non-smoker was not always clear and may sometimes have included former smokers. One study included a few smokers. The endpoints considered included asthmatic reactions (often as defined by a drop in FEV_1 of 20% or more), asthmatic symptoms, lung function and airway responsiveness.

Chapter 4 considers epidemiological studies that related indices of ETS exposure to endpoints that concern asthma severity or exacerbation in asthmatic non-smoking adults. These endpoints include acute exacerbations, severity and symptoms, drug use, quality of life and general health, lung function and bronchial responsiveness.

Chapter 5 considers epidemiological studies that related indices of ETS exposure to endpoints that concern asthma severity or exacerbation in asthmatic children. No restriction was made on smoking status, though many of the studies were based on children so young that smoking would effectively be ruled out, and some studies restricted attention to children who had never smoked, smoked no more than a minimum amount or did not currently smoke. Endpoints considered include hospitalisation, emergency room (ER) visits and urgent consultations, restricted activity, acute and non-acute asthma, asthma medication, health contacts for asthma, asthma severity, asthma symptoms and acute episodes, and quality of life and general health, as well as lung function and bronchial responsiveness.

Chapters 3, 4 and 5 follow a similar structure. In the first section, "The studies," they start by summarising the number of relevant publications and studies found, giving reasons why certain publications that seemed possibly relevant were not in fact considered. Then, for each study in turn, there follows a description of the study, including its design, location, number of subjects, and age, sex and smoking status of the subjects, and also a summary of the results. Next follows a summary of the main features of the combined set of studies.

The second section, "The results," summarises the results by endpoint and shows whether an association has been demonstrated convincingly.

The final section, "Summary and conclusions," brings all the material together and draws conclusions, and also includes a section which considers other published reviews of the evidence.

Chapter 6 then gives an overall assessment of the role of ETS exposure in asthma exacerbation based on the evidence described in chapters 3, 4 and 5.

2.3. ASTHMA INDUCTION

Chapters 7, 8 and 9 consider epidemiological studies of prevalent or incident asthma. After dealing with various general issues in chapter 7, chapter 8 is concerned with non-smoking adults, and chapter 9 with children with no restriction made on smoking status. Studies of children generally involved subjects aged up to age 18. Cross-sectional studies with a small proportion of subjects aged over 18, and prospective studies which had recruited the subjects when they were children and followed them into early adulthood were also considered to be of children. Unlike chapters 3, 4 and 5, which concern subjects who are asthmatic, chapters 7, 8 and 9 have no such restriction.

Only studies where the endpoint was "asthma" were included, and studies of "wheeze," "wheezing bronchitis," "chronic wheezing," "asthma or wheeze" or "asthmatic bronchitis" were excluded. Both chapters were intended to investigate the relationship of asthma both to indices of ETS exposure and to *in utero* exposure to maternal smoking, but in practice virtually no information on *in utero* exposure was available for adults.

It is important to realize that for many of the studies considered in chapters 8 and 9, the results cannot be strictly interpreted in terms of asthma induction. This is clearly so for cross-

sectional studies which collect information on whether the subject is currently asthmatic but not on the time of onset of asthma, where an association may be due to an effect on induction, exacerbation or a combination of both. This is discussed further in chapter 7, which elaborates further on methods and other issues generally relevant to the studies we have considered under the heading "asthma induction."

Whereas the approach to presentation and analysis of the exacerbation studies was generally a descriptive one, with no formal attempt made to extract all the data onto databases, the induction studies were approached in a different way.

Both for the studies in non-smoking adults and the studies in children, two linked databases were set up. One contains details of the characteristics of each study, while the other contains relative risk (RR) data relating to certain aspects of ETS and *in utero* exposure. The study database contains details of the study itself, the precise definition of asthma used and the potential confounding variables considered. The RR database contains not only each RR and 95% confidence interval (CI), but details of their definition and information on how they were derived. Chapter 7 gives fuller details on the structure of the databases, the methods used for entry and checking of data and for the derivation of RRs, as well as the techniques used to carry out meta-analyses.

Chapters 8 and 9 follow a similar structure. The first section, "The studies," starts by summarising the number of relevant publications and studies found, giving reasons why certain publications that seemed possibly relevant were not in fact considered. Except for those studies in children that potentially allow discrimination of effects of ETS and *in utero* exposure, the book does not directly contain a description of each study – due to the very large number of studies considered, particularly for children – but refers to a computer generated appendix that can be accessed via the internet. However a summary of the main features of the combined set of studies is given.

The second section, "The relative risks," summarizes some general characteristics of the RRs.

The third section, "The meta-analyses," presents the results of a range of analyses relating various definitions of asthma outcome to various indices of ETS exposure and, where appropriate, *in utero* exposure. The meta-analyses are aimed to give insight into how the RR of asthma varies by such factors as the source, timing and amount of ETS exposure (or parental smoking), the definition of the asthma outcome, the sex and age of the subject, the location, timing, size and type of study, the source of the information on exposure and diagnosis, and the extent of confounder adjustment.

The fourth section, "Discussion," starts by summarizing the evidence of an association and of a dose-response relationship, and then considers various issues relating to interpretation, including the consistency of the findings, publication bias, diagnostic bias, representativeness, misclassification of exposure, smoking by the subject, confounding, maternal smoking in pregnancy and inferences that can be drawn specifically relating to induction.

The final section, "Summary and conclusions," brings all the material together and draws conclusions, and also includes a section which considers some other published reviews of the evidence.

Chapter 10 then gives an overall assessment of the role of ETS exposure in asthma induction based on the evidence described in chapters 8 and 9.

2.4. Overall Conclusions

A summary of the main conclusions, with relevant comments, is given after chapter 10.

2.5. References

References cited are given at the end of each chapter.

2.6. Additional Information

At some points in the book, the availability of additional information on our website is referred to. This is accessed by *www.pnlee.co.uk/etsast.htm.* A listing of the various pieces of additional information is shown at the end of the Contents section of this book.

Chapter 3

EXACERBATION OF ASTHMA – EXPERIMENTAL EVIDENCE

3.1. THE STUDIES

3.1.1. Introduction

The literature searches identified about 25 independent studies which described the results of experimental chamber studies of the effects of ETS exposure on asthma in asthmatics, though as explained below there is some uncertainty as to the exact number of studies. Making up a substantial contribution to these studies were a series of papers published by a group from Tulane Medical School, New Orleans and another series published by a group from the Krankenhaus Grosshansdorf, Hamburg. However, one or two studies were also reported from eight other groups.

In sections 3.1.2 (New Orleans), 3.1.3 (Hamburg) and 3.1.4 (other), principal features of the various individual studies are described, including the subjects considered, the exposure and study design, and the types of endpoint (respiratory symptoms, airway responsiveness, lung function) for which results were available. Although the main conclusions of the authors are summarized, the detailed results are not considered until section 3.2. Section 3.1.5 summarizes various relevant aspects of the studies considered.

3.1.2. The New Orleans Studies

Based on a series of papers, abstracts and reports emanating from the group in New Orleans, eight apparently separate studies could be identified, some details of which are given in Table 3.1. Of the eight studies, details were not fully reported as a paper in four. Where details were presented, the studies were seen to be typically of never smokers or ex-smokers, though a few smokers were included in the final study (Lehrer et al., 1997), and female subjects outnumbered males. Some studies were of working age adults, but others included children. Seven of the eight studies were of subjects known to be sensitive to ETS exposure, with only the final study (Lehrer et al., 1997) apparently not making this restriction. Five of the eight studies exposed non-asthmatics as well as asthmatics.

Table 3.1. Some details of the New Orleans chamber studies

	Stankus et al., 1988	Menon et al., 1989	Menon et al., 1990	Menon et al., 1991a	Menon et al., 1991b	Lehrer, 1992	Menon et al., 1992	Lehrer et al., 1997
Reported as	Paper[1]	Abstract	Abstract	Abstract[2]	Paper[3]	Short report	Paper	Paper[4]
Asthmatics[5]								
- Total	21	11	10	100	15	163	31[6]	130
- By sex[7]	5M, 16F	?	?	?	3M, 12F	?	11M, 20F	37M, 93F
- By smoking[8]	13N, 8X	?	?	?	7N, 8X	?	26N, 5X	?[9]
- Age	21-50	?	12-18	?	25-51	?	12-50	18-60
- Atopic	19	?	?	?	All	?	All	All
Non-asthmatics[5]								
- Total	0	5	11	0	15	0	39	28
- By sex[7]		?	?		5M, 10F		17M, 22F	8M, 20F
- By smoking[8]		?	?		12N, 3X		36N,3X	?[9]
- Age		?	12-18		21-48		12-50	18-50
- Atopic		?	?		All		All	22
Data reported for								
- Asthma symptoms	Yes	No	Yes	No	No	No	No	No
- Airway responsiveness	No	Yes	Yes	No	No	No	Yes	No
- Lung function	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

[1] Essentially the same results were reported elsewhere in a conference paper (Stankus & Lehrer, 1988).

[2] A later abstract (Musmand et al., 1993) described results of allergy testing on presumably the same group of subjects.

[3] Essentially the same results were reported in abstracts (Menon et al., 1988; Lehrer et al., 1997).

[4] These data are cited elsewhere (Lehrer et al., 1999). It is possible that the short report of Lehrer, 1992 may be based on some of the subjects considered in this paper.

[5] Subjects were stated to be smoke-sensitive except for Lehrer et al., 1997.

[6] There were also another 10 “control” asthmatics who were not exposed, for whom details on age, sex and smoking habits were not given.

[7] M = males, F = females.

[8] N = never smoked, X = ex-smokers.

[9] Of the total of 158 subjects, asthmatic and non-asthmatic, 111 were never smokers, 30 were ex-smokers and 17 were smokers or had unknown smoking habits.

The earlier studies appeared to involve exposure to a mixture of mainstream and sidestream smoke derived by smoking a defined number of cigarettes via a Borgwaldt fully automatic smoking machine in a 26 m^3 static test chamber, though Menon et al. (1991a) referred to exposure to sidestream smoke. Two later studies (Lehrer, 1992; Lehrer et al., 1997) used a dynamic test chamber in which the smoking machine and other equipment were in an antechamber attached to the rear wall of the 16.9 m^3 test chamber. Mainstream smoke was exhausted from the antechamber, and the sidestream smoke concentration in the test chamber could be precisely controlled by varying the number of machine-smoked cigarettes

and adjusting the air flow. The first study (Stankus et al., 1988) used IR2F cigarettes supplied by the American Tobacco Institute, while, where this was reported, later studies used IR4F cigarettes from the Tobacco and Health Research Institute at the University of Kentucky.

Details of the study design and some further details of the exposure are given below:

Stankus et al., 1988

Subjects were exposed in a static chamber to up to three increasing levels of cigarette smoke (sidestream and mainstream):

Level	Aerosol (cpm)	Aerosol ($\mu g/m^3$)	CO (ppm)
Low	439	852	8.7
High	895	1421	13.3
Ultra high	1742	Not done	14.1

There was no sham exposure. Medication was withheld before testing (oral medication for 24 hours, inhaled bronchodilators for 8-12 hours, and steroids on the morning of challenge). Subjects were exposed to the low level for 2 hours. If a reaction (20% fall in forced expiratory volume in one second [FEV_1]) was not induced, they were then exposed to the high level for 2 hours, following a 30 minute rest period. Some subjects were then exposed later to the ultra high level if no reaction occurred.

Menon et al., 1989

Subjects were exposed in a static inhalation chamber, no details being given of the extent or duration of the exposure. There was no sham exposure. No details were provided as to whether medications were stopped. Serial methacholine challenges were performed and the provocative concentration to produce a 20% fall in FEV_1 (PC_{20}) was determined one day prior to, at 6 hours, at 24 hours and as necessary up to 14 days following smoke exposure. A two-fold or greater decline from baseline following smoke exposure was considered significant.

Menon et al., 1990

Subjects were exposed for four hours in a static chamber to a total suspended particulate concentration of 1394 $\mu g/m^3$. There was no sham exposure. No details were provided as to whether medications were stopped. There were methacholine challenges at 6, 24 and 72 hours and weekly post exposure. A two-fold or greater decline from baseline in PC_{20} following smoke exposure was considered significant.

Menon et al., 1991a

Subjects were exposed in a static chamber for up to 6 hours to suspended particulate concentrations of 1392, 804, 289 or 242 $\mu g/m^3$ (800, 400, 200 or 100 counts per minute [cpm]). No details were given as to whether medications were stopped. Those who reacted (with a 20% fall in FEV_1) were sham challenged (with no further details given) and then challenged sequentially at 4 week intervals to the decreasing dose levels.

Menon et al., 1991b

Subjects were exposed in a static chamber to a total suspended particulate concentration of 1145 μg/m^3 (800 cpm). Subjects avoided medication before exposures. The asthmatic subjects had a 2 to 6 hour exposure. Those who reacted (with a 20% fall in FEV_1) were subjected to a sham challenge for 6 hours. Those who did not react were subjected to a 6 hour challenge at the same smoke exposure 4 weeks later. The non-asthmatic subjects also underwent a 6-hour smoke challenge. Reactors were subsequently retested after pre-treatment with a bronchodilator, an anti-inflammatory medication, or both on three occasions 4 weeks apart.

Lehrer, 1992

Subjects were exposed in a dynamic chamber to a total suspended particle concentration of 750-2000 μg/m^3. Subjects were first challenged for up to 4 hours. Those who reacted (with a 20% fall in FEV_1) then underwent a 4 hour sham challenge. Some of those who reacted again were selected for dose-response challenge with decreasing levels of 804, 289 and 242 μg/m^3 ultra-violet (UV)-absorbing particulate matter for up to 6 hours at 4 week intervals. The study did not test for the possibility of reaction to sham exposure only without preceding smoke exposure.

Menon et al., 1992

Following withholding of asthma medication (12-24 hours depending on type), subjects underwent methacholine challenge. Next day, the 31 asthmatic and 39 non-asthmatic smoke-sensitive subjects were exposed for four hours in a static chamber to produce a mean total suspended particulate concentration of 1266 μg/m^3 (800 cpm). Study subjects demonstrating a reaction (20% fall in FEV_1) were allowed to leave the chamber. Lung function monitoring continued for 24 hours after exposure, and serial methacholine challenges were done after 6 and 24 hours, and in subjects showing an increase at 24 hours, at 3 days and then weekly. The 10 control asthmatics were not exposed to tobacco smoke, but no details were given whether they were sham exposed or not.

Lehrer et al., 1997

Subjects were exposed in a dynamic chamber at a smoke index corresponding to a UV particulate matter concentration of 1553 μg/m^3. Selected challenges were conducted at smoke indices of ½, ¼ and ⅛ of this. These produced UV particulate matter concentrations of 621, 337 and 121 μg/m^3. Medications were withheld for 24 hours prior to challenges. Subjects were first challenged with the high dose for up to 4 hours. Those who reacted (with a 20% fall in FEV_1) were allowed to leave the chamber, and then underwent a 4 hour sham challenge. Seven reactors to the sham challenge were then exposed for up to 4 hours to decreasing levels. The study did not test for the possibility of reaction to sham exposure without preceding smoke exposure.

Seven of the eight studies reported results for lung function, while three reported results for airway responsiveness and two reported results for asthma symptoms (see Table 3.1). The results will be described in detail in section 3.2, but Table 3.2 gives the main conclusions of the authors.

Table 3.2. Conclusions from the New Orleans chamber studies

Study	Conclusions of the authors
Stankus et al., 1988	"Collectively, these studies document a significant decline in pulmonary function in a substantial percentage (33%) of a population of 'smoke-sensitive' subjects with asthma exposed to environmental tobacco smoke."
Menon et al., 1989	"These results identify ETS as an important influence on airway reactivity and support our previous findings which documented significant declines in pulmonary functions in a substantial proportion of asthmatics after exposure to ETS."
Menon et al., 1990	"Although none of the 21 SS children had a significant decline in FEV_1, a significant number demonstrated increased sensitivity to methacholine, suggesting prolonged airway hyper-reactivity following ETSC." [SS is smoke-sensitive, ETSC is ETS challenge]
Menon et al., 1991a	"This study suggests that the level and duration of exposure play an important role in the development of asthmatic reactions following ETS exposure."
Menon et al., 1991b	"These studies demonstrate the persistence of ETS reactivity during a 2-year period."
Lehrer, 1992	"Our studies showed that about 10% of asthmatics claiming to be smoke sensitive actually demonstrated objective changes in their pulmonary function from high level SS-ETS exposure. These responses do not appear to be related to IgE antibody reactivity to tobacco allergens." [IgE is immunoglobulin E, SS is sidestream]
Menon et al., 1992	"Our studies of passive cigarette-smoke challenge in nonsmokers demonstrate that almost 1/3 of smoke-sensitive subjects with asthma and 1/5 of smoke-sensitive subjects without asthma have a marked increase in BHR 6 hours after ETS exposure." [BHR is bronchial hyperreactivity]
Lehrer et al., 1997	"Responses to diminishing levels of SS-ETS demonstrated that some asthmatics can react to levels as low as 0.0128 cigarette-min/m^3 (comparable to ETS levels in the homes of many smokers)." [SS is sidestream]

3.1.3. The Hamburg Studies

Based on papers and abstracts from the group in Hamburg, seven apparently separate studies could be identified, some details of which are given in Table 3.3. Of the seven studies, details were not fully reported in a paper in one. Studies were typically of never smokers[1], though a few ex-smokers were included in one study (Jörres & Magnussen, 1992). With the exception of the 91% of boys in the children included in the study by Oldigs et al. (1991) - children who were also probably included in the larger study of Magnussen et al. (1992) - numbers of males and females were similar. The asthmatics included in the studies were

defined as mild in five studies and as mild to moderate in two studies, and with minor exceptions were nearly all atopic. Two of the seven studies included a control group of healthy non-asthmatics.

Although not always fully reported, the exposure system appeared to be the same in each study, with subjects in a 24 m^3 chamber exposed to the smoke of filter cigarettes of a leading brand (nicotine 0.9 mg, tar 13 mg) smoked by a semi-automatic smoking machine. To ensure homogeneous concentration of cigarette smoke, the air was moved by fans with the chamber ventilated to ambient air (see e.g. Nowak et al., 1997a).

Table 3.3. Some details of the Hamburg studies

	Jörres et al., 1990	Oldigs et al., 1991	Jörres & Magnussen, 1992	Magnussen et al., 1992	Magnussen et al., 1993	Nowak et al., 1997a	Nowak et al., 1997b
Reported as Asthmatics	Abstract	Paper	Paper	Paper	Paper	Paper[1]	Paper[2]
- Total	11	11[3]	24	29	13	10	17
- By sex[4]	5M, 6F	10M, 1F	11M, 13F	18M, 11F	8M, 5F	6M, 4F	10M, 7F
- By smoking[5]	?	All N	20N,4X	All N	All N	All N	All N
- Age	Mean 36	8-13	15-66	8-51	8-13	22-29	19-38
- Asthma	Mild	Mild	Mild to moderate	Mild to moderate	Mild to moderate	Mild	Mild
- Atopic	?	All	22	All	All	All	All
Non-asthmatics							
- Total	0	0	16	16	0	0	0
- By sex[4]			7M, 9F	7M, 9F			
- By smoking[5]			13N, 3X	All N			
- Age			21-51	17-66			
- Atopic			8	All			
Data reported for							
- Asthma symptoms	Yes	Yes	Yes	Yes	Yes	Yes	Yes
- Airway responsiveness	Yes	Yes	Yes	Yes	Yes	No	Yes
- Lung function	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[1] The results were reported previously in an abstract (Nowak et al., 1995).

[2] The results were reported previously in an abstract (Nowak et al., 1993).

[3] The 11 children in the studies of Oldigs et al., 1991 and Magnussen et al., 1992 appear to be the same.

[4] M = male, F = female.

[5] N = never smoked, X = ex-smoker.

Details of the study design and further details of the exposure are given below:

[1] Note that some of the papers from the Hamburg group refer only to the term non-smokers but based on terminology used in other papers it appears that this term did not embrace ex-smokers.

Jörres et al., 1990

Subjects were exposed for 1 hour in a chamber on separate days to either ambient air or tobacco smoke (particulate matter concentration 2800 $\mu g/m^3$ and CO [carbon monoxide] 20 parts per million [ppm]). No details were given as to whether medications were stopped. On each day, symptoms and lung function were measured before and after exposure and a methacholine inhalation challenge was started 20 minutes after exposure.

Oldigs et al., 1991

Exposure was to a mean total suspended particulate concentration of 2743 $\mu g/m^3$ and a mean CO of 20.5 ppm. Each subject was studied on three days within a two week period, with all investigations performed at least six hours after last inhalation therapy. On the first day lung function and airway hyper-responsiveness were measured but there was no exposure. Day two was sham exposure and day three tobacco smoke exposure, each of 1 hour, with lung function measured before and immediately after each exposure and histamine inhalation challenge started 15 minutes after exposure. Except for one subject, medication was withheld for 6 hours before exposure.

Jörres and Magnussen, 1992

Exposure was to a particulate matter concentration of 3095 $\mu g/m^3$, and a CO of 20.3 ppm. Subjects were exposed for 1 hour on separate days to either ambient air or tobacco smoke, in random order. On each day, symptoms and lung mechanics were measured before and immediately after exposure and a methacholine inhalation challenge was started 20 minutes after exposure. Inhaled bronchodilators were withheld for 6 hours before exposure but other medication continued.

Magnussen et al., 1992

Exposure was to a mean particulate matter concentration of 2743 $\mu g/m^3$ and a mean CO of 20.5 ppm. Each subject was studied in a 2 week period. On two different days they were exposed for 1 hour to either tobacco smoke or ambient air. On each day, symptoms and lung function were measured before and immediately after exposure, and a methacholine (adults) or histamine (children) inhalation challenge was started 20 minutes after exposure. The asthmatic subjects continued corticosteroid medication as usual but refrained from using inhalation therapy for 6 hours before exposure. Note that the children in this study seem to be the same as in the paper reported by Oldigs et al. (1991).

Magnussen et al., 1993

Exposure was to a mean particulate concentration of 3197 $\mu g/m^3$ and a mean CO concentration of 20.2 ppm. Goggles were worn to prevent eye irritation. On separate days, the children were exposed to tobacco smoke or ambient air for 1 hour, with the order randomised. During the first 54 minutes, the children were at rest, and during the last 6 minutes they exercised on a bicycle ergometer. In seven children, the experiments with ambient air and tobacco smoke were done in duplicate. Symptoms were assessed before and 30 minutes after exposure. Lung function was measured serially during rest, during exercise and up to 25 minutes after. Bronchoactive medication was not used for 8 hours before exposure.

Nowak et al., 1997a

Exposure was to a particulate concentration of 3141 μg/m^3 and a CO level of 22.4 ppm. Subjects were studied on two different occasions at least 7 days apart, within a 2 week period. No ETS exposure had occurred at least 12 hours before the test. Subjects were exposed to tobacco smoke or ambient air in random order, for 3 hours in the evening. On-demand medications were withheld for 12 hours before the test. Symptoms were assessed at the start and end of exposure. Spirometry was conducted before, during and at end of exposure, then after 1 hour, 5 hours (i.e. 3 am) and 9 hours (i.e. 7 am next morning).

Nowak et al., 1997b

Exposure was to a particulate concentration of 3196 μg/m^3 and a CO level of 22.4 ppm. Subjects were studied on two occasions at least 7 days apart, within a 2 week period. No ETS exposure had occurred at least 12 hours before the test. Subjects were exposed to tobacco smoke or ambient air in random order, for 3 hours between 7 and 10 pm. Serial measurements (spirometry, methacholine challenge and symptom assessment) were made for up to 9 hours (i.e. to 7 am next day). The final symptom assessment was made after 24 hours. On-demand medications were withheld for 12 hours before test.

Except for one study that did not report results for airway responsiveness (Nowak et al., 1997a), all the studies reported results for asthma symptoms, airway responsiveness and lung function. Table 3.4 gives the main conclusions of the authors.

Table 3.4. Conclusions from the Hamburg studies

Study	Conclusions of the authors
Jörres et al., 1990	"We conclude that in mild asthmatics short-term exposure to ETS does not exert a consistent effect on lung function and bronchial responsiveness."
Oldigs et al., 1991	"Our observations suggest that in children with mild bronchial asthma 1 hour of passive cigarette smoking does not cause consistent changes of lung function and bronchial responsiveness."
Jörres & Magnussen, 1992	"Our observations suggest that in healthy subjects and in patients with mild to moderate asthma, symptoms induced by one hour of passive smoking are not explained by changes in lung mechanics and airway responsiveness."
Magnussen et al., 1992	"Our observations suggest that in children and adults with mild to moderate bronchial asthma, 1 h of passive cigarette smoking does not cause airway obstruction or consistent changes in bronchial responsiveness."
Magnussen et al., 1993	"In children with mild asthma, short-term exposure to ETS can be associated with a transient fall in FEV_1 in sensitive subjects but does not increase exercise-induced bronchoconstriction."
Nowak et al., 1997a	"Our data demonstrate that a single ETS exposure in subjects with mild asthma causes symptoms which were not accompanied by detectable changes in lung function or inflammatory changes immediately and several hours after exposure."
Nowak et al., 1997b	"Our data show that in some subjects with mild asthma, exposure to a high concentration of passive smoke in the evening can induce nocturnal symptoms and lung function changes compared to a control exposure. These changes are largely independent of each other and appear not to be associated with a history of ETS-induced symptoms."

Table 3.5. Some details of the other chamber studies

	Shephard et al., 1979	Urch et al., 1988	Ing & Breslin, 1983	Knight & Breslin, 1985	Dahms et al., 1981	Ben Hassine et al., 1984	Wiedemann et al., 1986	Ortega Gonzalez et al., 1989	Gurk et al., 1991	Danuser et al., 1993
Reported as	Paper	Paper	Abstract	Paper	Paper	Paper	Paper	Paper	Abstract	Paper
Location	Toronto, Canada	Toronto, Canada	Sydney, Australia	Sydney, Australia	St Louis, USA	Tunis, Tunisia	New Haven, USA	Mexico	Munster, Germany	Zurich, Switzerland
Asthmatics										
- Total	14	16	6	6	10	11	9	62	20	10[3]
- By sex[1]	9M, 5F	8M, 8F	?	4M, 2F	?	All F	5M, 4F	48M, 14F	?	4M, 6F
- By smoking[2]	?	13N, 3X	?	All NS	All NS	All NS	All NS	All NS	?	All NS
- Age	19-65	19-63	?	22-39	18-26	Mean 32	19-30	6-16	Mean 36	24-50
- Other details	4 smoke-sensitive	-	Mild to moderate asthma, all smoke-sensitive	Mild to moderate asthma, 4 smoke-sensitive	5 smoke-sensitive	-	6 smoke-sensitive	-	-	8 smoke-sensitive
Controls										
- Total	0	24	0	0	10	9	0	0	9	10
- By sex[1]		12M, 12F			?	All F			?	4M, 6F
- By smoking[2]		20N, 4X			All NS	All NS			?	All NS
- Age		18-34			24-53	Mean 32			Mean 34	24-52
- Other details		6/12 smoke-sensitive			5 smoke-sensitive	-			-	2 smoke-sensitive
Data reported for										
- Asthma symptoms	Yes	No	Yes	Yes	No	No	Yes	No	No	Yes
- Airway responsiveness	No	No	No	Yes	No	No	Yes	No	Yes	No
- Lung function	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[1] M = males, F = females.

[2] N = never smoked, X = ex-smoker, NS = non-smoker (not otherwise defined).

[3] These 10 subjects were only defined as being hyperreactive, but 5 had asthma and 4 of the remainder had symptoms suggestive of asthma.

3.1.4. The Other Studies

Table 3.5 gives some details of the remaining 10 studies. Two of these were reported only as an abstract. Where details were provided, the studies appeared to be all of current non-smokers, though the extent to which they might have included ex-smokers was very often undefined. With the exception of the Tunisian study (Ben Hassine et al., 1984), which was only of females, the studies generally included both sexes, predominantly males in the Mexican study (Ortega Gonzalez et al., 1989), but more equally divided in the others. The Mexican study was of children, but other studies were of adults. Five studies included non-asthmatic control groups. One study (Ing & Breslin, 1983) restricted attention to subjects who reported being sensitive to smoke, but though a number of other studies presented numbers reporting such sensitivity, no other study appeared to have such a restriction.

Eight of the 10 studies involved exposure to cigarette smoke produced mechanically, but in two (Ben Hassine et al., 1984; Ortega Gonzalez et al., 1989), the exposure was to smokers in the room. In the studies in Toronto (Shephard et al., 1979; Urch et al., 1988) and in the study in Zurich (Danuser et al., 1993), the smoke was generated outside the room and passed into it. In other studies, the smoke was either produced mechanically in the room (Ing & Breslin, 1983) or no details were given as to where the smoking took place. One study (Danuser et al., 1993) made it clear that exposure was specifically to sidestream smoke, with two other studies (Dahms et al., 1981; Gurk et al., 1991) reporting that exposure was to sidestream, but providing no details as to how the mainstream smoke had been removed. Other studies seemed to have exposed subjects to a mixture of sidestream and mainstream smoke. The tar and nicotine levels of the cigarettes smoked were often not reported, and where they were were sometimes totally implausible. Thus, while plausible values (per cigarette) of 16 mg tar, 1.6 mg nicotine were reported by Ing & Breslin (1983) and of 15 mg tar, 1.1 mg nicotine by Danuser et al. (1993), implausible values of 19 mg tar, *14 mg* nicotine were reported by Shephard et al. (1979) and of 15 mg tar, *0.15 mg* nicotine by Dahms et al. (1981). Probably these were typographical errors for *1.4 mg* and *1.5 mg* nicotine, respectively.

Details of the study design and further details of the exposure are given below:

Shephard et al., 1979

Subjects were exposed in a closed room of 14.6m^3 to a CO concentration of 24 ppm above ambient and a suspended particulate concentration of 2-4 mg/m^3. The subjects were in the room for two hours on two occasions – ambient air or smoke exposed. The order of the two tests was randomized. Subjects continued with their normal medication on experimental days.

Urch et al., 1988

Subjects were exposed in a 14.6m^3 chamber to “moderate” smoke (17 ppm CO) or “heavy” smoke (31 ppm CO). On Visit 1 baseline physiological and psychological data were obtained but there was no exposure. On Visits 2 to 4 subjects were exposed for 65 minutes to either heavy, moderate or sham exposure, with the order of treatments balanced. On these three visits, subjects were shown a similar bank of burning cigarettes. Asthmatics rested during exposures, but non-asthmatics exercised intermittently on a bicycle. Asthmatics continued their usual medication, except during exposure. The main objective of the study

was to investigate whether suggestibility may augment any physiological response to tobacco smoke.

Ing and Breslin, 1983

Exposure was in a 7m^3 room to concentrations of smoke in the range 20-25 ppm CO, with rises in carboxyhaemoglobin (COHb) of 0.5%. Each subject was in the room for one hour on two occasions, exposed to ambient air first and to smoke second. Subjects abstained from medications for 6 to 48 hours prior to tests, the time depending on the medication.

Knight and Breslin, 1985

Subjects *were "exposed to the air of a provocation room in which smoke was produced mechanically from one cigarette after another, continuously, over one hour,"* with no further details given. Exposure may be as described by Ing & Breslin (1983). No details are given as to whether medications for asthma were stopped pre-test. Each subject was in the room for one hour on two occasions, exposed to ambient air first and to smoke second.

Dahms et al., 1981

Exposure was in a 30m^3 chamber which produced an average increase in COHb of 0.40%, taken to indicate an environmental CO concentration of 15 to 20 ppm. Subjects in both groups were exposed in the chamber for 1 hour with lung function measured before exposure and at 15 minute intervals during exposure. There was no sham exposure. The asthmatic subjects continued taking their medication but refrained from using any bronchodilators for four hours before exposure.

Ben Hassine et al., 1984

Exposure was in a 34m^3 unventilated room, the smoke being generated by two smokers smoking continuously in the room. COHb levels rose following exposure from 0.71 to 1.2% in the asthmatics and from 0.84 to 1.1% in the controls. There was no sham exposure. Two subjects were exposed at a time for an hour. Spirometry was conducted at the start of exposure, after 15, 30, 45 and 60 minutes of exposure, and also 10 minutes after the end of exposure after a dose of an adrenergic bronchodilator (salbutamol). Medication had been ceased for at least 12 hours before the start of exposure.

Wiedemann et al., 1986

Exposure was in a 4.25m^3 chamber to a mean CO level of 40 to 50 ppm. Subjects were given the option to wear goggles to reduce eye irritation. There was no sham exposure. Methacholine inhalation challenge and spirometry was recorded on day 1. On day 2 spirometry was recorded before a 1 hour tobacco smoke exposure, with methacholine inhalation challenge and spirometry immediately after. Subjects refrained from using inhaled bronchodilators for 6-8 hours before exposure.

Ortega Gonzalez et al., 1989

Exposure was in a 35m^3 furnished room where two volunteers smoked a total of five cigarettes. There was no measurement of smoke constituent levels and no sham exposure. Subjects were exposed for an hour, with lung function measured before and after exposure.

Bronchodilator medication was suspended 8 hours before the study, with antihistamines suspended by as much as 72 hours in some cases.

Gurk et al., 1991

Exposure was in a chamber to produce 35-40 ppm CO. There was no sham exposure. Lung function was measured before and immediately after exposure for an hour. Histamine challenge was performed on the day before and 20 minutes after exposure in all asthmatics to determine the provocative concentration to produce a 100% increase in specific airway resistance (PC_{100}SRAW). No details were provided as to whether the medications were stopped.

Danuser et al., 1993

Subjects were exposed to serially increasing 2 minute exposures to sidestream smoke delivered via a mouthpiece. CO concentrations were successively 0, 2, 4, 8, 16 and 32 ppm (± 5%) above ambient (average 2.4 ppm). There was 5-7 minutes rest between successive exposures. Subjects wore nose-clips during exposure. Subjects could not see the smoking machine and were not told about the increasing dose. Lung function measurement and methacholine challenge test was carried out on day 1 (pre-test). On day 2 (experimental; within 4 days of the pre-test), lung function was measured 30 and 90 seconds after each exposure and provocation was terminated if there was a fall in FEV_1 of 20% or more from the value after 0 ppm inhalation. A symptom questionnaire was completed after each level of exposure. Subjects refrained from taking oral medication for 48 hours and inhaled bronchodilators for 12 hours before test.

All the 10 studies reported results for lung function, while six reported results for asthma symptoms and three reported results for airway responsiveness (see Table 3.5). Table 3.6 gives the main conclusions of the authors.

3.1.5. Summary of the Studies

In this section various aspects of the studies and their designs are summarized.

Incomplete reporting. Of the 25 studies summarized in sections 3.1.2 to 3.1.4, six (Ing & Breslin, 1983; Menon et al., 1989; Menon et al., 1990; Jörres et al., 1990; Gurk et al., 1991; Menon et al., 1991a) were described only in abstracts, and five (Ben Hassine et al., 1984; Knight & Breslin, 1985; Ortega Gonzalez et al., 1989; Lehrer, 1992; Magnussen et al., 1992) only relatively briefly, in papers of four pages or less. This contributes to the fact that it was not always possible to obtain all the relevant details for each study.

Possible overlaps between studies. Although the 25 papers summarized in Tables 3.1, 3.3 and 3.5 have been treated as if they were separate studies, it is possible that they do not all describe completely different studies. Thus a short report in 1992 from the New Orleans group (Lehrer, 1992) may be a description of the same study described more fully in 1997 (Lehrer et al., 1997). The numbers of subjects differ between the two reports, but it is possible the later report excluded some of the subjects originally referred to. The short report of Lehrer (1992) seems also to overlap to some extent with the study reported by Menon et al. (1991a). Though the total numbers of subjects differ, both studies describe identical results from a

dose-response sub-study of seven subjects who reacted to high dose exposure. Furthermore, it is reasonably clear that the 11 children referred to in a 1992 paper from the Hamburg group (Magnussen et al., 1992) are the same as those referred to in a 1991 paper from the same group (Oldigs et al., 1991). The 1992 paper also includes results for adults.

Table 3.6. Conclusions from the other chamber studies

Study	Conclusions of the authors
Shephard et al., 1979 Toronto, Canada	"Changes of pulmonary function were slight. Our data thus do not suggest that asthmatic subjects have an unusual sensitivity to cigarette smoke."
Urch et al., 1988 Toronto, Canada	"Significant dose-response relationships … observed for reported symptoms, deterioration of pulmonary function … could reflect either a pure physiological response, or an interaction between physiological and psychological responses."
Ing & Breslin, 1983 Sydney, Australia	"Passive exposure to cigarette smoke in these subjects produced marked symptoms described as usual asthma but not significant evidence of airways obstruction."
Knight & Breslin, 1985 Sydney, Australia	"Our findings suggest that passive smoke inhalation may produce asthma attacks in subjects who suffer from asthma and may lead to increased bronchial reactivity to histamine for a time after such inhalation."
Dahms et al., 1981 St Louis, USA	"These data show that nonsmokers with bronchial asthma are at risk when exposed to sidestream cigarette smoke in an environmental chamber."
Ben Hassine et al., 1984 Tunis, Tunisia	"In summary, our conventional spirometric measures were incapable of detecting a systematic bronchomotor reaction of ETS inhalation on the bronchi of either asthmatics or control subjects with undamaged lung pathology. Clinically one suspects nevertheless an aggravating effect of passive smoking in asthmatics. More precise measures of breathing are probably necessary to verify this interaction." [Translated from French]
Wiedemann et al., 1986 New Haven, USA	"Although the finding of decreased airway reactivity might suggest that passive smoking produces a 'protective' effect on the underlying asthma, the observed change in reactivity was slight and of uncertain clinical significance. We conclude that passive smoking presents no acute respiratory risk to young asymptomatic asthmatic patients."
Ortega Gonzalez et al., 1989 Mexico	"The results obtained for the effects of passive smoking should not be considered conclusive … The most sensitive parameter of the spirometry test was the MMEFR." [Translated from Spanish]
Gurk et al., 1991 Munster, Germany	"We conclude that passive exposure to sidestream cigarette smoke may reduce lung function in sensitive asthmatics. Furthermore these subjects are at risk of developing an increase in airway reactivity to histamine."
Danuser et al., 1993 Zurich, Switzerland	"Even short exposure to low concentrations of cigarette sidestream smoke causes significant impairment of lung function in sensitive persons."

Number of subjects. The papers citing the largest number of subjects are three from the New Orleans Group: Lehrer (1992) involving 163 asthmatics; Lehrer et al. (1997) involving 130 asthmatics and 28 non-asthmatics; and Menon et al. (1991a) involving 100 asthmatics. The next largest is the 62 children study in Mexico (Ortega Gonzalez et al., 1989). Other papers all describe small studies ranging from six subjects in the Sydney studies (Ing & Breslin, 1983; Knight & Breslin, 1985) to 31 in one of the other New Orleans studies (Menon et al., 1992).

Asthma status. Subjects were generally mild to moderate asthmatics, and had been free of respiratory infections or asthma exacerbations for at least several weeks before the study.

Age. Four of the studies were of children (Ortega Gonzalez et al., 1989; Menon et al., 1990; Oldigs et al., 1991; Magnussen et al., 1993), with two studies (Menon et al., 1992; Magnussen et al., 1992) involving both adults and children. Other studies were of adults.

Gender. Seven studies (Dahms et al., 1981; Ing & Breslin, 1983; Menon et al., 1989; Menon et al., 1990; Gurk et al., 1991; Menon et al., 1991a; Lehrer, 1992) gave no details on the gender of the subjects. One study (Ben Hassine et al., 1984) was of females only. Other studies included both males and females. (In general, results were not presented separately by age or gender.)

Smoking status. Most studies were restricted to non-smokers, although the definition of non-smoker was not always clear and may have included former smokers. Indeed it was stated to do so in some of the New Orleans studies (Stankus et al., 1988; Menon et al., 1991b; Menon et al., 1992), and also in one of the Toronto studies (Urch et al., 1988) and one of the Hamburg studies (Jörres & Magnussen, 1992). One New Orleans study (Lehrer et al., 1997) included a few smokers and some where smoking status was not known – of the total of 158 subjects, 111 were stated never to have smoked and 30 were stated to have been ex-smokers for at least four years. A number of studies did not define the smoking status of their subjects.

Sensitivity to smoke. The New Orleans group generally restricted attention to subjects with a perceived sensitivity to smoke. Other studies usually included only a proportion who considered themselves sensitive, though this was not always known.

Healthy controls. Thirteen of the papers did not refer to any healthy control group. A further two studies (Dahms et al., 1981; Urch et al., 1988) used controls of very different ages from the asthmatics, while the remaining ten studies (Ben Hassine et al., 1984; Menon et al., 1989; Menon et al., 1990; Gurk et al., 1991; Menon et al., 1991b; Jörres & Magnussen, 1992; Menon et al., 1992; Magnussen et al., 1992; Danuser et al., 1993; Lehrer et al., 1997) used control groups which were either directly matched on age and gender or at least of a comparable distribution. It should be pointed out, however, that though the presence of a healthy control group allows comparison of the effects of exposure in asthmatics and non-asthmatics, failure to observe a difference between the two groups does not in theory actually allow the inference that exposure does not have an effect, as there may be an effect in both groups.

Exposure. In the Zurich study (Danuser et al., 1993) a smoking machine was kept in a small chamber not visible to the participants, the subjects wore nose clips and had the tobacco smoke administered by mouthpiece. In the other studies subjects breathed normally in the chamber. In two studies (Ben Hassine et al., 1984; Ortega Gonzalez et al., 1989) smokers smoked in the chamber, while in others a smoking machine was used, in some cases the cigarettes being burnt in the room, in others the cigarettes being burnt outside with the smoke piped through. Though from the material presented in the papers this was not always clear, it

appears that in most studies exposure was to a mixture of sidestream and mainstream smoke. However in three studies (Lehrer, 1992; Danuser et al., 1993; Lehrer et al., 1997) it was made clear that the subjects were only exposed to sidestream smoke and in three other studies (Dahms et al., 1981; Gurk et al., 1991; Menon et al., 1991a) they might have been. Note that none of the studies involving tobacco smoke generated by machines exposed subjects to what can strictly be defined as ETS, which is a mixture of sidestream smoke and exhaled mainstream smoke.

Reporting of the cigarettes used in the studies was limited. Standard research cigarettes were used in the New Orleans studies and a "leading brand" of filter cigarettes was used in the Hamburg studies. In the other studies details were often not provided and where they were provided, were sometimes implausible (see section 3.1.4).

In some studies the chamber was remarkably small, 4.25 m^3 (Wiedemann et al., 1986) and 7 m^3 (Ing & Breslin, 1983). The New Orleans and Hamburg groups used larger chambers of about 25 m^3. Subjects appear to have been seated during exposure, with two exceptions: in Urch et al. (1988) the healthy control group exercised and in Magnussen et al. (1993) the subjects exercised for the last 6 minutes.

Level of smoke constituents. Levels of particulate matter and/or CO were reported in all but two studies (Ortega Gonzalez et al., 1989; Menon et al., 1989). Concentrations of particulate matter in homes where smokers are present are typically less than 100 $\mu g/m^3$ and though levels may be higher in some restaurants and bars, reported mean levels rarely exceed 300 $\mu g/m^3$ or so (National Cancer Institute, 1993). Particulate matter concentrations were reported in 15 of the 25 papers summarized. They always exceeded 1000 $\mu g/m^3$ and in the Hamburg studies were typically around 3000 $\mu g/m^3$ at the maximum dose levels tested. It was clear, therefore that what was generally being tested was not typical but quite extreme exposure. The same is true for CO, where levels of 20 to 30 ppm were usually reported, perhaps 10 times higher than those found in everyday environments where real-life exposure to ETS may occur (Scherer et al., 1992). The extreme nature of the exposures in some studies was illustrated by the subjects wearing goggles (Magnussen et al., 1993) or having the option to wear them (Wiedemann et al., 1986).

Sham exposure. 16 of the 25 papers described using a sham exposure. The exceptions were the studies in St. Louis (Dahms et al., 1981), Tunis (Ben Hassine et al., 1984), Munster (Gurk et al., 1991), New Haven (Wiedemann et al., 1986) and Mexico (Ortega Gonzalez et al., 1989), and four of the studies in New Orleans (Stankus et al., 1988; Menon et al., 1989; Menon et al., 1990; Menon et al., 1992) although this last study briefly mentioned an extra group of 10 subjects not exposed to ETS who may have been sham-exposed.

Time of exposure. Exposure was for 1 hour in the first five Hamburg reports (Jörres et al., 1990; Oldigs et al., 1991; Jörres & Magnussen, 1992; Magnussen et al., 1992; Magnussen et al., 1993) and in eight other studies (Dahms et al., 1981; Ing & Breslin, 1983; Ben Hassine et al., 1984; Knight & Breslin, 1985; Wiedemann et al., 1986; Urch et al., 1988; Ortega Gonzalez et al., 1989; Gurk et al., 1991). Apart from the Zurich study, which only exposed through a mouthpiece for 2 minutes at each dose level (Danuser et al., 1993), other studies had longer exposure. Thus, the two final Hamburg studies (Nowak et al., 1997a; Nowak et al., 1997b) involved 3 hours exposure, four New Orleans studies (Menon et al., 1990; Menon et al., 1992; Lehrer, 1992; Lehrer et al., 1997) involved 4 hours exposure, and two other New Orleans studies (Menon et al., 1991a; Menon et al., 1991b) up to 6 hours exposure. With the

exception of the Zurich study (Danuser et al., 1993) the length of exposure in all the studies was longer than would be normal for either methacholine or antigen challenge.

Variation in exposure levels. Most of the studies tested only a single exposure level of ETS. However, three of the New Orleans studies (Menon et al., 1991a; Lehrer, 1992; Lehrer et al., 1997) involved a high exposure of around 1500 $\mu g/m^3$ particles and further exposures of about ½, ¼ and ⅛ of this, while another New Orleans study (Stankus et al., 1988) had a ½ exposure and, for selected subjects, an exposure of twice the standard level. One of the Toronto studies (Urch et al., 1988) had two exposure levels, producing 31 and 17 ppm CO, while the mouthpiece study in Zurich (Danuser et al., 1993) started with a dose equivalent to ambient air (0 ppm CO), and then successively increased the exposure to 2, 4, 8, 16, 32 ppm above this. The low exposures in some of the studies with varying levels will be more typical of real-life high level scenarios.

Stopping of medication by the subjects. Where stated, the procedure in the Hamburg series of studies was to discontinue inhalation therapy for at least 6 hours (Oldigs et al., 1991; Jörres & Magnussen, 1992; Magnussen et al., 1992) or at least 12 hours (Nowak et al., 1997a; Nowak et al., 1997b) before exposure. In the earlier New Orleans studies (Stankus et al., 1988; Menon et al., 1992), inhaled bronchodilators were stopped 8 to 12 hours before each test, with participants instructed to avoid theophylline oral sympathomimetic medications for 24 hours before. In the last one (Lehrer et al., 1997), medications were withheld for 24 hours prior to the challenge, with antihistamines withheld for 48 to 72 hours. In only three studies (Shephard et al., 1979; Dahms et al., 1981; Urch et al., 1988) was medication stated to be continued, though not all studies reported details of this.

Statistical issues. Suppose that a lung function (or other) variable has values measured for a particular subject of:

E_o baseline measurement for smoke exposure
E_t time t measurement for smoke exposure
S_o baseline measurement for sham exposure
S_t time t measurement for sham exposure

A correct statistical analysis of the data would then involve calculating a response to smoke (e.g. E_t-E_o or E_t/E_o) and a response to sham exposure (e.g. S_t-S_o or S_t/S_o) and using a paired statistical test to determine whether the responses to smoke and sham exposure differ. In practice, a number of the papers considered here have not used, or not been able to use, appropriate statistical tests.

In some studies (e.g. Dahms et al., 1981; Wiedemann et al., 1986; Stankus et al., 1988; Ortega Gonzalez et al., 1989) sham exposure has not been tested at all, in some (e.g. Ing & Breslin, 1983) sham exposure data have not been reported, while in others (e.g. Lehrer, 1992; Lehrer et al., 1997) being sham exposed depended on the subject having a previous reaction to tobacco smoke exposure, with further dose-response studies being restricted to those who did not react to sham exposure. Furthermore others have not always used appropriate statistical tests. Thus, for example, one paper (Shephard et al., 1979) separately tested whether E_t/E_o differed from 1 and whether S_t/S_o differed from 1, a procedure which may miss an effect if, for example, the data show a non-significant decrease for E_t/E_o and a non-significant increase for S_t/S_o. Similarly, another paper (Knight & Breslin, 1985) tested for significance within each subject (by a procedure which was not clearly described) but did not

perform any proper overall test based on the differences in response for each subject. In this paper, it was easy enough to do the appropriate test as the individual subject data were available, but this is not always so. Other problems with the statistical analyses include failure to present results of any significance tests, or individual data from which these could be calculated, (e.g. Ben Hassine et al., 1984), use of Bonferroni-corrected tests (Oldigs et al., 1991; Magnussen et al., 1992) rather than simple uncorrected tests of the difference between the exposed and the sham-exposed groups, and failure to present appropriately the results of paired analyses (e.g. Magnussen et al., 1993; Nowak et al., 1997a; Nowak et al., 1997b), giving means and standard errors (SEs) separately for the two groups rather than for the difference between groups.

For any differences in response seen not to be attributed to other causes it is also important for the ordering of the sham exposure visit and the tobacco smoke exposure visit to be randomized, or at least to be approximately equally divided between subjects. However, it was clear that this was far from the general situation. Varying the ordering of the two exposures was carried out in some studies (Shephard et al., 1979; Urch et al., 1988; Jörres & Magnussen, 1992; Magnussen et al., 1993; Nowak et al., 1997a; Nowak et al., 1997b) but not in others (Ing & Breslin, 1983; Knight & Breslin, 1985; Oldigs et al., 1991; Danuser et al., 1993).

It is relevant to note that none of the 25 papers describe studies involving a smoke-exposed and a sham-exposed group, where the ordering of the exposure was randomized, where the proper statistical analysis was conducted, and where the results were presented in an appropriate manner.

3.2. RESULTS

3.2.1. Symptoms of Asthma

A number of studies did not report results for symptoms, or only discussed results for symptoms such as eye and nasal irritation, which, though clearly affected by tobacco smoke exposure, are not indicative of asthma. Studies which determined cough, chest tightness, wheezing or difficulty in breathing, all symptoms that are associated with an attack of asthma (National Cancer Institute, 1999), and which reported results were as follows:

Stankus et al., 1988

All seven subjects in whom a significant decline in FEV_1 was seen also reported some symptoms of asthma following tobacco smoke exposure. There was no sham exposure.

Menon et al., 1990

Subjects complained of cough, wheezing or chest tightness following tobacco smoke exposure. There was no sham exposure.

Jörres et al., 1990

The only symptom noted to occur during tobacco smoke exposure was eye irritation. Precisely which symptoms were recorded was not stated.

Oldigs et al., 1991

There was no significant difference in respiratory symptoms between tobacco smoke and sham exposure.

Jörres & Magnussen, 1992

There was a significant difference between tobacco smoke and sham exposure for tightness of the chest but not for cough.

Magnussen et al., 1992

There was some excess in cough and chest tightness following tobacco smoke exposure in adults but not in children.

Magnussen et al., 1993

Symptoms of asthma were non-significantly higher following tobacco smoke exposure than following sham exposure.

Nowak et al., 1997a

Tobacco smoke exposure significantly increased a generalized score for symptoms of the throat and chest.

Nowak et al., 1997b

Tobacco smoke exposure significantly increased a generalized score for symptoms of the throat and chest, an increase which did not remain evident some hours following exposure.

Shephard et al., 1979

Symptoms of asthma were reported by some subjects following tobacco smoke exposure, but no results were reported following sham exposure.

Ing and Breslin, 1983

All six subjects reported chest tightness following tobacco smoke exposure but not following sham exposure ($p<0.05$).

Knight and Breslin, 1985

All six subjects reported some symptoms of asthma following tobacco smoke exposure, but no results were presented for sham exposure.

Wiedemann et al., 1986

Three tobacco smoke exposed subjects reported a mild cough. There was no sham exposure.

Danuser et al., 1993

There was an apparent dose-related increase in cough and chest tightness.

The evidence is somewhat variable, perhaps due to small sample sizes and differences in methodology. However, the data, taken as a whole, clearly indicate that tobacco smoke exposure can induce those symptoms which occur during an attack of asthma.

3.2.2. Airway Responsiveness

Of the 11 studies that reported results following challenge by methacholine or histamine, four reported an *increase* in airway responsiveness following tobacco smoke exposure.

In one of these (Knight & Breslin, 1985), PC_{20}, in all six subjects, fell more over the four hour period of exposure than on the sham exposure day ($p<0.05$). The changes were still detectable four hours after tobacco smoke exposure.

In the three other studies (Menon et al., 1989; Menon et al., 1990; Menon et al., 1992) a proportion of asthmatics (5/10, 3/10 and 5/31 respectively) were reported to show an increase in bronchial responsiveness following tobacco smoke exposure. This increase was regarded as clinically significant. However clinically significant increases were also seen in some non-asthmatic controls (1/5, 4/11 and 0/31 respectively), and there was no sham exposure.

In contrast, Wiedemann et al. (1986) reported a significant ($p=0.04$) *decrease* in airway responsiveness following tobacco smoke exposure. There was no sham exposure in this study either.

All the remaining studies (Jörres et al., 1990; Oldigs et al., 1991; Gurk et al., 1991; Jörres & Magnussen, 1992; Magnussen et al., 1992; Nowak et al., 1997b) found no significant effect of tobacco smoke, although one of these (Gurk et al., 1991) reported a mild increase in bronchial reactivity ($p=0.038$) in those asthmatics with more than a 5% decrease in FEV_1. Another study (Magnussen et al., 1993) found no effect on exercise-induced bronchoconstriction.

Overall, the data do not show any very clear effect of tobacco smoke exposure on airway responsiveness in asthmatics.

Table 3.7. Change in FEV_1 in relation to tobacco smoke exposure[1]

Study (Location)	Result
Jörres et al., 1990 (Hamburg)	Mean changes in FEV_1 following tobacco smoke exposure (+0.12ℓ) and following sham exposure (-0.03ℓ) did not differ significantly.[2]
Oldigs et al., 1991 (Hamburg)	There was no difference (in children) between pre- and post-exposure FEV_1 following either tobacco smoke exposure (1.95ℓ vs 1.94ℓ) or sham exposure (1.97ℓ vs 1.98ℓ).
Jörres & Magnussen, 1992 (Hamburg)	Changes following tobacco smoke exposure (3.34ℓ pre to 3.21ℓ post) did not differ significantly from those following sham exposure (3.28ℓ pre to 3.24ℓ post).
Magnussen et al., 1992 (Hamburg)	Changes following tobacco smoke exposure (3.31ℓ pre to 3.21ℓ post) did not differ significantly from those following sham exposure (3.18ℓ pre to 3.14ℓ post). These are results for adults. Results for children as reported in Oldigs et al., 1991.

Table 3.7. Continued

Study (Location)	Result
Magnussen et al., 1993 (Hamburg)	The change in FEV_1 in the children during tobacco smoke exposure (1.68ℓ pre to 1.56ℓ during) was significantly (p=0.043) greater than the change during sham exposure (1.66ℓ pre to 1.61ℓ during).
Nowak et al., 1997a (Hamburg)	There was no significant change in FEV_1 during or after tobacco smoke exposure as compared with sham or pre-exposure levels, e.g. 3.79ℓ, 3.63ℓ, 3.72ℓ at start, end and 1 hour after tobacco smoke exposure, and 3.66ℓ, 3.63ℓ, 3.59ℓ for sham exposure.
Nowak et al., 1997b (Hamburg)	There was a greater fall with tobacco smoke exposure than with sham exposure both during exposure (5.6% vs 3.0%, p=0.013) and after exposure (9.1% vs 5.9%, p=0.026).
Shephard et al., 1979 (Toronto)	Ratio of exposed to sham FEV_1 1.031 at baseline, 1.021 after 30 mins, 0.992 after 1 hour, 1.021 after 90 mins and 1.014 after 2 hours. Variation not significant.
Urch et al., 1988 (Toronto)	Change in FEV_1 from pre-exposure levels after 30 mins exposure were +23 ml for sham, +4 ml for *"moderate"* tobacco smoke (17 ppm CO) and – 71 ml for *"heavy"* tobacco smoke (31 ppm CO). The dose-response was significant (p<0.05).
Ing & Breslin, 1983 (Sydney)	No significant changes in FEV_1 when compared to baseline values. [Sham exposure data not reported.]
Knight & Breslin, 1985 (Sydney)	All 6 subjects showed a fall in FEV_1 following tobacco smoke exposure but none did following sham exposure (p<0.05).
Dahms et al., 1981 (St Louis)	Percent reduction in FEV_1 following tobacco smoke exposure 8.6% after 15 mins (not significant), 12.9% after 30 mins (p<0.01), 17.5% after 45 mins (p<0.01) and 21.4% after 1 hour (p<0.01). [No sham exposure.]
Ben Hassine et al., 1984 (Tunis)	Percent change in FEV_1 following tobacco smoke exposure +1.2% after 15 mins, +2% after 30 mins, -1.2% after 45 mins and +1.1% after 60 mins. All the changes were not significant. [No sham exposure.]
Wiedemann et al., 1986 (New Haven)	FEV_1 was similar on day 1 at baseline (3.43ℓ), on day 2 pre-smoke (3.48ℓ) and on day 2 post-smoke (3.45ℓ). [No sham exposure.]
Gurk et al., 1991 (Munster)	Significant decline in FEV_1 from 3.02ℓ to 2.89ℓ (p<0.025) following tobacco smoke exposure. [No sham exposure.]
Danuser et al., 1993 (Zurich)	No difference in FEV_1 between pre-test and baseline (0 ppm). Following exposure at 2, 4, 8, 16 and 32 ppm CO percent reductions in FEV_1 were, respectively, 6.5, 5.6, 7.1, 8.2 and 8.7%. The effect of tobacco smoke was highly significant (p<0.001) but not clearly dose-related.

[1] Details of the exposures are given in section 3.1.

[2] Here, and subsequently, not significant implies p≥0.05.

3.2.3. Lung Function

FEV_1 is the lung function variable that has been the most studied. Some studies have carried out statistical analyses based on the average change in FEV_1 following tobacco smoke exposure, while others (notably the New Orleans group) have investigated the proportion of subjects "reacting" (showing a fall of 20% or more in FEV_1).

Table 3.7 summarizes the results for average FEV_1 while Table 3.8 summarizes the results for the proportion reacting.

Table 3.8. Proportion of asthmatics "reacting" (showing a 20% or more fall in FEV_1) in relation to tobacco smoke exposure[1]

Study (Location)	Result
Stankus et al., 1988 (New Orleans)	Of the 21 subjects, 2 (9.5%) reacted to low exposure (852 $\mu g/m^3$ particulates) and a further 5 (23.8%) reacted to high exposure (1421 $\mu g/m^3$ particulates). All the reactions were reproducible on re-challenge. Of the remaining 14, 5 claiming a strong history of smoke sensitivity were tested at an ultra-high exposure level (about twice the high exposure) and none reacted. [No sham exposure.]
Menon et al., 1990 (New Orleans)	None of the 10 children reacted following exposure. [No sham exposure.]
Menon et al., 1991a (New Orleans)	Of the 100 subjects, 7 (7.0%) reacted at high exposure (1392 $\mu g/m^3$ particulates). Of these, 3 did not react to any of the three lower dose levels (804, 289, 242 $\mu g/m^3$ particulates), 1 reacted only to the highest of these doses, and 3 reacted to all three doses.
Menon et al., 1991b (New Orleans)	6 subjects had been shown to react to tobacco smoke 2 years earlier. Of these, 5 again reacted on re-challenge after 1 to 2 hours exposure. None of the 5 reacted to sham challenge. The sixth subject did react on a subsequent occasion after 2½ hours. The other 9 subjects had previously not reacted and did not react again after challenges of 2 and 6 hours duration on 2 separate days 4 weeks apart.
Lehrer, 1992 (New Orleans)	Of the 163 subjects, 28 (17.2%) reacted to tobacco smoke exposure. 11 of these also reacted to sham challenge, but 17 did not. 7 of these 17 underwent a dose-response study with the results reported the same as for Menon et al., 1991a shown above.
Menon et al., 1992 (New Orleans)	Of the 31 asthmatics, 5 (13%) reacted to tobacco smoke. None of the 39 asthmatic controls reacted to sham exposure.

Table 3.8. Continued

Study (Location)	Result
Lehrer et al., 1997 (New Orleans)	Of the 130 asthmatics, 26 (20%) reacted to the high exposure (1553 μg/m^3 particulates). Of the 26 reactors, 6 (23%) reacted to sham exposure also. Of the 20 who reacted to tobacco smoke only, 7 underwent a dose-response study at lower levels of 621, 337 and 121 μg/m^3 particulates. 3 did not react at all, 1 reacted only at the highest of these 3 doses; 1 reacted at the highest 2 of these doses, and 2 reacted at all 3 lower doses.
Oldigs et al., 1991 (Hamburg)	Of the 11 children, 1 (9.1%) reacted to tobacco smoke exposure. None reacted to sham exposure.
Jörres & Magnussen, 1992 (Hamburg)	Of the 24 adults, 1 (4.2%) reacted to tobacco smoke exposure. None reacted to sham exposure.
Magnussen et al., 1993 (Hamburg)	Of the 13 children, 2 (15.4%) reacted to tobacco smoke exposure. None reacted following sham exposure.
Nowak et al., 1997a (Hamburg)	Of the 10 subjects, none reacted to tobacco smoke exposure during the 3 hour exposure period or 9 hours afterwards.
Nowak et al., 1997b (Hamburg)	Of the 17 subjects, 5 (29%) reacted between 1 and 9 hours following tobacco smoke exposure. 1 of these also reacted to sham exposure. 1 subject reacted only to sham exposure, but 9 hours after the end of exposure.
Ing & Breslin, 1983 (Sydney)	No subjects reacted, the largest fall noted being 12.55%. [Sham exposure data not reported.]
Knight & Breslin, 1985 (Sydney)	Of the 6 subjects, 1 (16.7%) reacted following tobacco smoke exposure. There were no falls following sham exposure.
Dahms et al., 1981 (St Louis)	The proportion reacting was not reported, but as average changes were around 20% after 45 mins and 1 hour exposure it is clear that many subjects, perhaps at least 50%, reacted. [No sham exposure.]
Wiedemann et al., 1986 (New Haven)	None of the 9 subjects reacted following exposure. [No sham exposure.]
Ortega Gonzalez et al., 1989 (Mexico)	Of the 62 children, (3.2%) reacted following tobacco smoke exposure. [No sham exposure.]
Danuser et al., 1993 (Zurich)	1 of 10 subjects (10%) reacted to 16 ppm CO. [None reacted at baseline (0 ppm) compared with pre-test.]

[1] Details of the exposures are given in section 3.1.

Of the 16 studies considered in Table 3.7, significant effects on FEV_1 were reported in seven (Dahms et al., 1981; Knight & Breslin, 1985; Urch et al., 1988; Gurk et al., 1991; Danuser et al., 1993; Magnussen et al., 1993; Nowak et al., 1997b). The studies which found no significant effect were all small (ranging from 6 to 24 subjects) and it is possible that a lack of significance might occur due to lack of power. This may be particularly relevant if an effect is only seen in a small proportion of reactive subjects, who might not even be present at all in some of the studies. Note that results for the New Orleans studies are not included in Table 3.7 as their principal endpoint was reaction, and mean FEVs were not presented.

The series of studies in New Orleans (Stankus et al., 1988; Menon et al., 1990; Menon et al., 1991a; Menon et al., 1991b; Menon et al., 1992; Lehrer, 1992; Lehrer et al., 1997) reported results which were together consistent with the following conclusions:

- There are a proportion of asthmatics who react to tobacco smoke exposure;
- Some of these also react to sham exposure;
- Disregarding those who also react to sham exposure, asthmatics who react tend to react again following rechallenge to the same exposure;
- Reaction is dose-related. Some asthmatics who react at high doses do not react at lower doses, but others react consistently at all the doses tested, down to levels similar to high environmental exposure;
- Reaction is also time-related, and may not be seen until after a few hours of exposure especially at lower dose levels; and
- Non-asthmatics rarely, if ever, show such reactions.

Occasional reactions following exposure were also seen in the studies in St. Louis (Dahms et al., 1981), Mexico (Ortega Gonzalez et al., 1989) and Zurich (Danuser et al., 1993) and in one of the studies in Sydney (Knight & Breslin, 1985). The other Sydney study (Ing & Breslin, 1983) and the New Haven study (Wiedemann et al., 1986) did not have any reactors, but included only six and nine subjects, respectively.

Two early studies in Hamburg (Oldigs et al., 1991; Jörres & Magnussen, 1992), which claimed no effect of tobacco smoke on FEV_1, did in fact include some reactors (as can be seen from the individual subject data), as did a later study (Magnussen et al., 1993) which reported a marginally significant effect. These studies were of 1 hour duration, less than the period of exposure which produced many of the reactions seen in the New Orleans studies. Of two later studies in Hamburg, involving a 3 hour exposure period, one (Nowak et al., 1997a), of 10 subjects, found no reactors, while the other, of 17 subjects, found five (Nowak et al., 1997b).

The question as to the relative effects of tobacco smoke and sham exposure on the probability of reaction is an important one. Though the New Orleans studies found that only some subjects who reacted to tobacco smoke also reacted to sham exposure, they did not test all subjects for the effects of sham exposure, and one does not know how many subjects might have reacted to sham exposure and not tobacco smoke. The other studies, however, cast some light on this. Thus four studies (Knight & Breslin, 1985; Oldigs et al., 1991; Jörres & Magnussen, 1992; Magnussen et al., 1993) found reactions only with tobacco smoke exposure, while one study (Nowak et al., 1997b) found more reactions to tobacco smoke exposure only than to sham exposure only.

Results for lung function variables other than FEV_1 were reported in 11 studies and are summarized in Table 3.9. As in Table 3.7, results for the New Orleans studies are not included as only FEV_1 was studied. In general, the results summarized in Table 3.9 are very similar to those summarized in Table 3.7. Overall the data for lung function variables other than FEV_1 do not materially assist further in deciding whether or not the overall data show that tobacco smoke exacerbates asthma.

Table 3.9. Summary of findings for lung function measurements[1] other than FEV_1 in relation to tobacco smoke exposure[2]

Study (Location)	Result
Jörres et al., 1990 (Hamburg)	No significant[3] effects on SRAW following exposure.
Oldigs et al., 1991 (Hamburg)	There was no difference (in children) between pre- and post-exposure SRAW following either tobacco smoke exposure (10.4 vs 9.4) or sham exposure (8.7 vs 9.0).
Jörres & Magnussen, 1992 (Hamburg)	Changes in SRAW following tobacco smoke exposure (7.9 pre to 7.4 post) did not differ significantly from those following sham exposure (8.2 pre to 7.9 post).
Magnussen et al., 1992 (Hamburg)	Changes in SRAW following tobacco smoke exposure (7.5 pre to 7.2 post) did not differ significantly from those following sham exposure (8.8 pre to 8.4 post). These are results for adults. Results for children as reported in Oldigs et al., 1991.
Shephard et al., 1979 (Toronto)	No significant differences between tobacco smoke and sham exposure after 2 hours for RVC, RV, FRC, FVC, $VMAX_{25\%}$ or $VMAX_{50\%}$. Only significant effect on TLC (ratio of smoke to sham 0.965, $p<0.02$). Ratios were also not significant for the dynamic lung volumes after 30, 60 and 90 minutes, except for FVC (ratio of smoke to sham 1.039, $p<0.05$). Changes in pulmonary function were considered to be *"slight."*
Urch et al., 1988 (Toronto)	Changes from pre-exposure levels after 30 minutes tobacco smoke exposure were as follows:

	FVC	*$FEF_{50\%}$*	*$FEF_{75\%}$*	*$FEF_{60\%iso}$*
Sham	0	+56	+16	+24
Moderate	-41	+69	+59	+29
Heavy	-105	0	-4	-104
Trend p	<0.05	NS	NS	NS

Ing & Breslin, 1983 (Sydney)	Falls of 20% or more in FVC and PEFR and of 30% in MMEFR were defined as *"significant"* but none were observed. One subject showed a 26.8% fall in MMEFR. [Sham exposure data not reported.]
Knight & Breslin, 1985 (Sydney)	Trends in VC, MMEFR and PEFR were noted to be *"similar"* to those seen for FEV_1. [Data not reported.]
Dahms et al., 1981 (St Louis)	Following tobacco smoke exposure percent reductions in FVC and $FEF_{25-75\%}$ were similar to those noted for FEV_1 (see Table 3.7) and significant ($p<0.05$ or $p<0.01$). [No sham exposure.]
Ben Hassine et al., 1984 (Tunis)	Compared to pre-exposure levels, levels following exposure after 15, 30, 45 and 60 minutes were, respectively, -0.5%, +0.7%, +0.5% and –0.5% for VC and +2.0%, -11.7%, -4.2% and –5.4% for $FEF_{25-75\%}$. Statistical tests were not conducted. [No sham exposure.]
Wiedemann et al., 1986 (New Haven)	$VMAX_{50\%}$ was similar on day 1 at baseline (3.46), on day 2 pre-smoke (3.46) and on day 2 post-smoke (3.42). Corresponding FVC values were 4.57, 4.65 and 4.56. The decrease (2%) following exposure was statistically significant ($p<0.01$). [No sham exposure.]

Table 3.9. (Continued)

Study (Location)	Result
Ortega Gonzalez et al., 1989 (Mexico)	20%+ declines in MMEFR were seen in 8/62 of the children (13%), with 10-20% declines in a further 6 (9.7%). For FVC 20%+ declines were seen in 1 (1.6%), with 10-20% declines in a further 2 (3.2%). [No sham exposure.]
Gurk et al., 1991 (Munster)	There was a significant increase in SRAW from 5.29 to 5.96 (p=0.033) following tobacco smoke exposure. [No sham exposure.]
Danuser et al., 1993 (Zurich)	Following exposure at 2, 4, 8, 16 and 32 ppm CO reductions in FVC and MEF_{50} were seen which were evident, and highly significant p<0.001) at all dose levels but only slightly greater at higher than at lower doses. [Sham exposure data not reported.]

[1] Abbreviations used in Table 3.9 are as follows:

$FEF_{x\%}$	Forced expiratory flow at x% of forced vital capacity
$FEF_{x\%iso}$	Forced expiratory flow at x% of forced vital capacity as measured pre-exposure
FEV_1	Forced expiratory volume in one second
FRC	Functional residual capacity
FVC	Forced vital capacity
MEF_{50}	Maximal expired flow rate at 50% of FVC
MMEFR	Mid-maximal expiratory flow rate
PEFR	Peak expiratory flow rate
RV	Residual volume
RVC	Relaxed vital capacity
SRAW	Specific airway resistance
TLC	Total lung capacity
VC	Vital capacity
$VMAX_{x\%}$	Maximum volume at x% of vital capacity

[2] Details of the exposures are given in section 3.1.

[3] Here, and subsequently, not significant implies $p \geq 0.05$.

3.2.4. A Physiological or a Psychological Response?

For the purposes of deciding whether or not tobacco smoke exacerbates asthma, it does not particularly matter whether the response is a physiological or a psychological one. However some of the studies reported data relating to this issue.

In the second Toronto study (Urch et al., 1988) subjects viewed a bank of burning cigarettes during each of sham, moderate and heavy tobacco smoke exposure, and data on psychological and subjective response variables were recorded. The authors concluded from their findings (not considered here in detail) that *"while suggestibility may augment physiological responses to passive smoking, any effect is relatively weak."* It seems to us that if the sight of the burning cigarettes during sham exposure was supposed *"to provide an element of suggestion"* it should have been controlled for by a visit involving sham exposure and no sight of the burning cigarettes.

The fact that in the large studies in New Orleans (Lehrer, 1992; Lehrer et al., 1997) some asthmatics reacted to sham exposure with a 20%+ drop in FEV_1 indicates that responses may not always be due to a physiological reaction to cigarette smoke constituents.

Reports of a lack of association between a positive smoke challenge and either the presence of serum IgE antibodies or a positive immediate wheal-and-flare skin test to a tobacco leaf extract (Stankus et al., 1988; Ortega Gonzalez et al., 1989; Lehrer, 1992) suggest that the response is not a clinical allergic response.

3.3. SUMMARY AND CONCLUSIONS

3.3.1. Summary

About 25 experimental chamber studies have been conducted in which asthmatic subjects have been exposed to tobacco smoke for between 1 and 6 hours, many of the studies being conducted by two groups, one in New Orleans and one in Hamburg. In most cases the exposure was from a smoking machine, and was not strictly ETS, being either sidestream smoke only or a mixture of mainstream and sidestream smoke, and not including a contribution from exhaled mainstream smoke. The studies generally involved an exposure which is much higher than encountered even in extreme environmental conditions, with typical particulate concentrations in the range 1000-3000 $\mu g/m^3$ and CO concentrations exceeding 20 ppm. Some of the studies involve multiple dose levels with the lowest levels tested more typical of high environmental exposure. The majority of the studies involve a sham exposure.

Although three papers reported results (possibly from the same study) in groups of 100 or more asthmatics, the great majority of the studies reported results from small groups, about half with 12 subjects or less. Most studies were of adults, though a few involved children. Current smokers were, with minor exceptions, excluded from the studies, but some studies included some ex-smokers. Details of some of the studies were inadequately reported and proper statistical analyses were often not conducted.

The series of studies in New Orleans, and particularly the largest and most recent data, provide strong evidence that there is a proportion of asthmatics who react to exposure by a drop in FEV_1 of 20% or more. Reaction (and non-reaction) could be consistently demonstrated, and reaction was shown to be dose- and time-related. While some subjects only reacted at high doses, a few reacted at all the dose levels tested. Though some subjects also reacted to sham exposure (implying that in these subjects the smoke exposure itself may not be causing the reaction), there are a proportion of subjects who react to smoke but not sham exposure. While the design of the New Orleans studies did not allow one to assess how many subjects reacted to sham but not tobacco smoke exposure, other studies with relevant data suggest that this is a much rarer event. The actual proportion of asthmatics who react to tobacco smoke exposure in this way cannot be estimated precisely due to the non-random selection of the asthmatics in the studies (e.g. as smoke-sensitive by self report in the New Orleans studies, and as mild to moderate in the Hamburg studies), but is likely to be quite low. Thus, in the latest New Orleans study, 15% of the smoke-sensitive subjects reacted to tobacco smoke exposure (and not sham exposure) at the highest exposure level tested, and the proportion reacting at typical environmental levels would be substantially less than this. While some studies did not report finding any reactors, this may have been due to the few subjects who were tested or to the insufficient length of tobacco smoke exposure.

The evidence relating symptoms to tobacco smoke exposure is somewhat variable, perhaps due to the small sample sizes and the differences in methodology, between studies, but the data taken as a whole clearly indicate that tobacco smoke exposure can induce those symptoms (cough, chest tightness, wheezing, difficulty in breathing) which occur during an attack of asthma.

The data do not show any clear effect of tobacco smoke exposure on airway responsiveness. Nor do they show any relation between reaction (FEV_1 decline), and either the presence of IgE serum antibodies or a positive wheal-and-flare skin test.

3.3.2. Other Published Reviews of the Evidence

A number of other reviews have considered some of the evidence described in Chapter 3 (Coultas, 1998; Weiss et al., 1999; National Cancer Institute, 1999; Jaakkola & Jaakkola, 2002; Eisner, 2002; International Agency for Research on Cancer, 2004; California Environmental Protection Agency, 2005; Eisner, 2005). Perhaps the most comprehensive is that by the California EPA (National Cancer Institute, 1999) which considered data from 10 of the studies described here (Shephard et al., 1979; Dahms et al., 1981; Knight & Breslin, 1985; Wiedemann et al., 1986; Stankus et al., 1988; Oldigs et al., 1991; Menon et al., 1991b; Menon et al., 1992; Danuser et al., 1993; Magnussen et al., 1993) and which concluded:

> "In summary, although the design constraints of the chamber studies limit the interpretation of the results, they do suggest that there is likely to be a subpopulation of asthmatics who are especially susceptible to ETS exposure. The physiological responses observed in these investigations appear to be reproducible in both 'reactors' and 'nonreactors.' It is unlikely that the physiological and symptomatic responses reported are due exclusively to either stress or suggestion."

This general conclusion was echoed by the other reviewers. The limitations of the evidence were discussed in that report and also in some of the other reviews (e.g. Weiss et al., 1999; Jaakkola & Jaakkola, 2002). For example, the review of Jaakkola & Jaakkola (2002) pointed out:

> "The results of the experimental studies have been somewhat inconsistent, and their interpretation is hampered by small sample sizes, differences in the selection criteria applied to recruit asthmatics, variable exposure times (ranging from 1 to 6 hours), and variable methods used to assess outcome. Controlled chamber exposure studies have the strengths of measuring exposure and outcome more precisely than is usually possible in epidemiologic studies. On the other hand, they have the following weaknesses that reduce their sensitivity to detect any effects of environmental tobacco smoke on asthma: (i) only those with stable asthma can be exposed, although asthmatics in poor control are probably more sensitive to adverse effects, (ii) asthmatics with a recent respiratory infection are often excluded, although these subjects are likely to be more sensitive, and (iii) exposure periods are often short."

Though these points are valid, they all give the reader the impression that the chamber studies have underestimated the true risk to the asthmatic non-smoker. It is of interest that this review, and indeed *none* of the other reviews cited above, actually mentioned the important

fact that the chamber studies were typically conducted at exposure levels that were very much higher than encountered in real-life situations, even in smoky bars.

3.3.3. Conclusion

The experimental studies demonstrate that tobacco smoke exposure can exacerbate asthma in a subset of susceptible individuals. For the great majority of asthmatics, however, tobacco smoke exposure, even at extremely high concentrations, does not appear to cause asthmatic attacks.

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Chapter 4

EXACERBATION OF ASTHMA – EPIDEMIOLOGICAL EVIDENCE IN ADULTS

4.1. THE STUDIES

4.1.1. Introduction

The literature searches identified 10 publications which described the results of epidemiological studies in adults specifically relating indices of ETS exposure to endpoints that concern asthma severity or exacerbation in non-smokers. Three of the publications describe studies conducted in Chandigarh, India (Jindal et al., 1994; Jindal et al., 1996; Jindal et al., 1999) while one describes a study in 8 regions of Switzerland (Künzli et al., 2000). The remaining six publications describe studies conducted in the USA, one nationwide, based on NHANES III (Eisner, 2002b), one in Denver (Ostro et al., 1994), one in Portland (Sippel et al., 1999) and the other three based on a study conducted in northern California (Eisner et al., 1998; Eisner et al., 2001; Eisner et al., 2002). One of the publications is only an abstract (Jindal et al., 1996).

A further 13 publications described studies that seemed possibly relevant, but in fact did not meet the inclusion criteria specified. The reasons for rejection included no data collected on ETS exposure (Speer, 1968; Abramson et al., 1995), no results reported relating ETS exposure to aggravation of asthma (Dales et al., 1992), results not reported for non-smokers (Bailey et al., 1990; Hong et al., 1994; Tarlo et al., 2000; Bayona et al., 2002), results not reported for asthmatics (Blanc et al., 1999), results not reported for asthmatic non-smokers (Lebowitz, 1984a; Lebowitz, 1984b; Connolly et al., 1989; Upton et al., 1998) and response is in relation to ETS exposure during travel, but the exposure variable relates to ETS exposure elsewhere (Eisner & Blanc, 2002).

The studies are described individually in section 4.1.2, starting with those conducted in Chandigarh, and ending with the US studies. Section 4.1.3 summarizes various relevant aspects of the studies considered, and section 4.2 brings together the findings by type of endpoint.

4.1.2. Description of the Studies

The Chandigarh Studies

The first study in Chandigarh (Jindal et al., 1994) compared indices of morbidity and control of severity in 100 adult never smoking asthmatics who were not exposed to ETS at home or at work and 100 adult never smoking asthmatics who were exposed. The ETS-exposed group were of mean age 39.5 years and the unexposed group were of mean age 33.8 years. These were stated to be comparable but based on the standard deviations given (9.90 and 10.03) are highly significantly different ($p<0.001$). The sex of the patients was undescribed. Information on asthma control and morbidity was assessed during their follow-up visits in the chest outpatient clinic by inquiring into emergency department visits, hospitalisation, acute episodes, requirement of parenteral drugs at home, corticosteroids and maintenance bronchodilators in the preceding 1-year period. Lung function was recorded by the measurement of forced expiratory flows on the same day as the follow-up visit. Subjects were excluded if they had been hospitalised or had a severe acute attack in the preceding 2 weeks.

The authors reported a number of statistically significant reductions in the ETS-exposed group. For FEV_1 (68.7% vs 80.8%), FEV_1/FVC (63.5% vs 78.4%) and $FEF_{25-75\%}$ (54.3% vs 75.7%) the reductions were stated to be significant at $p<0.05$, but are actually highly statistically significant ($p<0.001$) based on the standard deviations presented. For maintenance bronchodilator requirement daily (66% vs 56%), maintenance bronchodilator requirement intermittent (56% vs 42%) and steroid requirement intermittent (56% vs 42%) the increases in frequency in the ETS-exposed group were stated to be significant at $p<0.01$, but are not even significant at $p<0.05$. (It should be noted that the data for frequency of maintenance bronchodilator requirement for the ETS-exposed group seem impossible. How can 66% of the patients have a daily and 56% an intermittent requirement, since 66% + 56% = 122%?) Also claimed are significant ($p<0.01$) excesses in the ETS-exposed group for emergency department visits (0.82 vs 0.6), acute episodes (1.32 vs 0.6), number of parenteral bronchodilators (8.6 vs 6.0), weeks absent from work (3.6 vs 3.0) and weeks requiring steroids (11.3 vs 8.6). Here the data presented are not sufficient to check the significance levels.

Though the authors claimed that *"the control of asthma is poor and morbidity greater in adult patients with asthma exposed to ETS at home and/or at work"* failure to age adjust and obvious errors in statistical analysis mean that one cannot have any confidence in these findings.

In the second study in Chandigarh, reported in an abstract (Jindal et al., 1996), exposure to ETS in the preceding 24 hours was compared in 100 non-smoking patients with acute exacerbation of asthma and another 100 with stable non-acute asthma. The authors reported that *"There was a significant higher ($p<0.01$) prevalence of exposure to ETS in patients with acute exacerbations. Quantitatively, measured in 'man-hours', there was a higher exposure in this group. Sixty percent asthmatics had one or other symptom on acute exposure to ETS"* and concluded that "*Exposure to ETS causes acute worsening in non-smoker asthmatics."* No further details of the findings were presented.

In the third study in Chandigarh (Jindal et al., 1999) a bronchial provocation test using histamine was performed on 50 asthmatic adult women aged 20-40 years. While the abstract stated that they were "*nonsmokers,"* the methods section stated that they were enrolled

"without any knowledge of their smoking history" and that *"most women were likely to be nonsmokers."* 23 of the patients had a history of ETS exposure from the husband. There was no significant difference between the exposed and unexposed women in either FEV_1 (77.9 vs 79.4%) or FEV_1/FVC (83.6 vs 86.3%). PD_{20}, the dose of histamine to produce a 20% fall or greater in FEV_1, was lower in the ETS-exposed group (5.66 vs 11.80), a difference the authors estimated as significant at $p<0.01$ but we do not since, based on the standard deviations given (9.62 and 13.06), the t-value is only 1.91 ($p>0.05$). The authors also claimed a significant difference in the proportion of patients requiring continuous bronchodilator therapy, with 9/23 (39%) in the ETS-exposed group as against 7/27 (26%) in the unexposed group. This difference is in fact far from statistically significant. Also noted are a non-significant increase in the mean number of acute episodes in the previous year in relation to ETS exposure (4.83 vs 4.00) – which clearly is non-significant – and a statistically significant difference in PD_{20} according to an ETS exposure index calculated by multiplying years of exposure by daily hours of exposure. Here the significance of the difference in PD_{20} (1.8 units for index >15 and 3.2 units for index >0 but <15) cannot be checked from the information presented, but clearly cannot be trusted. The authors' claim of an association of ETS exposure with bronchial responsiveness, which in any case is based on analyses with no adjustment for potential confounding variables, must be regarded as extremely doubtful.

The Swiss SAPALDIA Study

Based on the *S*wiss Cohort Study on *A*ir *P*ollution *a*nd *L*ung *D*iseases *i*n *A*dults (SAPALDIA) study, a multicentre study involving eight areas in Switzerland, analyses were presented relating ETS exposure at work to lung function in 3,534 lifelong never smoking adults with acceptable spirometry. 325 were asthmatics, either doctor-diagnosed asthma or wheeze without cold in last 12 months, of mean age 40 years, with 44% male (Künzli et al., 2000). The main results relating to the asthmatic subjects are summarized below:

		% changes (95% CI) in lung function measures associated with ETS exposure at work[1]		
Subjects	n	FVC	FEV_1	$FEF_{25-75\%}$
All	325	-1.7(-5.5 to +2.1)	-4.8(-9.2 to +0.0)	-12.4(-20.4 to -3.7)
Male	142	+1.4(-4.0 to +7.1)	+0.5(-7.9 to +9.6)	-1.4(-18.0 to +18.5)
Female	183	-4.4(-9.6 to +1.1)	-8.7(-14.5 to -2.5)	-20.8(-32.0 to -7.6)
Female: BR[2]=no	66	Not given	-1.7(-9.4 to +6.7)	-4.7(-19.4 to +12.6)
: BR=yes or not measured	117	Not given	-12.3(-19.9 to -3.9)	-30.6(-43.4 to -14.8)

[1] Adjusted for log age, log age squared, log height, ETS at home, occupational gas/dust/smoke, and area of residency.

[2] Bronchial reactivity to methacholine.

The results show no evidence of a relationship of ETS exposure at work to FVC. The data also show no significant relationship to FEV_1 or $FEF_{25-75\%}$ in males, but some evidence of a reduction in females, particularly in those who are bronchially reactive or for whom bronchial reactivity could not be measured, mostly due to obstructive pre-test conditions. Additional analysis on extent of ETS exposure among those exposed only at work found a significant dose-response with FEV_1 and $FEF_{25-75\%}$, but only among asthmatic women. The authors considered that *"differences in the level of [ETS] exposure may be the main reason*

for the observed sex pattern." However, sampling variation may also be the explanation, as the differences between men and women in the % change estimates are not statistically significant for either FEV_1 or $FEF_{25-75\%}$ ($0.05<p<0.1$).

The Northern California Study

Three relevant publications have been based on a cohort study conducted in Northern California, USA. In the first of these (Eisner et al., 1998), analyses were presented based on 451 non-smoking adults with asthma who were attending pulmonary or allergy clinics. They were aged 18-50 (mean 40 years) and 30% male, and answered questions on ETS exposure and other variables at baseline and at an 18 month follow-up. ETS exposure was based on questions concerning regular exposure to tobacco smoke at home, work or in other locations over the past 12 months (baseline) or past 18 months (follow-up). Four groups of subjects were defined: I. No exposure at either time (n=322); II. Exposure at baseline only (n=43); III. Exposure at follow-up only (n=56); and IV. Exposure at baseline and follow-up (n=30). A wide variety of analyses were presented.

The first set of analyses concerned baseline ETS exposure only, comparing groups II and IV combined vs groups I and III combined. After adjusting for age, sex, race and income, ETS exposure was associated with a significant increase in asthma-related health care use over the previous 12 months, in terms of emergency department visits (odds ratio [OR] = 2.1, 95% CI 1.2-3.5), urgent physician visits (1.9, 1.1-3.3) and hospitalisations (1.9, 1.02-3.6). Restricted activity days were reported to have been recorded, but results were not presented. ETS exposure was also associated with significantly higher asthma severity (p=0.03), worse asthma-specific quality of life (AQOL) (p=0.04) and worse general health status as indicated by physical scores (p=0.04) but not mental scores.

Another set of analyses concerned changes in asthma outcomes within groups between baseline and follow-up, after adjustment for age, sex, race, income and baseline asthma severity. Within group II, those who had ceased being ETS exposed, there was a significant reduction in asthma severity (p=0.0003), no significant change in AQOL, and a significant improvement in health status as indicated by physical scores (p=0.05), but not mental scores. Within group III, those who had started being ETS exposed, there was no significant worsening in any of these four asthma outcomes. Nor were there any significant changes in group IV, who had continued ETS exposure.

A third set of analyses related the probability of health care use to exposure cessation, initiation and continuation after adjustment for age, sex, race, income and baseline asthma severity. The only statistically significant relationships noted were between cessation and reduced emergency department visits (OR = 0.4, 95% CI 0.2-0.97) and reduced hospitalisations (0.2, 0.04-0.97). It is unclear here precisely what comparisons are being made. If the comparisons are being made within group, how has adjustment been made for the differing periods to which the health care use refers (12 months vs 18 months)? If the comparisons are being made between groups, what reference group is being used in each case?

The authors stated that *"In conclusion, self-reported ETS exposure is associated with greater asthma severity, worse health status, and increased health care utilization in adults with asthma."*

The study has limitations, including relatively small numbers of subjects in some of the groups of interest, inadequate description of some analyses, and perhaps failure to present

analyses which more generally relate change in ETS exposure to change in asthma endpoint using the data from all the subjects at once. Nevertheless it is clearly superior to many of the other studies on asthmatic adults described in section 4.1.2. One interesting feature of the data which might have merited more detailed coverage is the observation that adjustment for covariates substantially reduced the strength of the association of cessation with asthma outcomes. For example, adjustment changed the improvement in asthma severity score from 3.2 to 1.9 points, and made non-significant the improvement in AQOL. Which covariates caused the marked changes in the estimates? Could adjustment for other covariates have reduced the estimates further?

A further publication (Eisner et al., 2001) was based on 50 asthmatic adults recruited from the Northern California study, who reported no current personal tobacco smoking and a positive answer to any screening question indicating potential ETS exposure. The recruited subjects, who were of mean age 44.4 years, with 28% male, wore a passive nicotine monitor for 7 days. Compared to the 21 subjects with no measured nicotine, those subjects with a high level of nicotine (>0.05 $\mu g/m^3$) had a significantly increased risk of respiratory symptoms (odds ratio 6.8, 95% CI 1.4-32.3) and of extra bronchodilator use (8.1, 1.3-50). Subjects with a lower level of nicotine (>0-0.05 $\mu g/m^3$) had a non-significant increase of both respiratory symptoms (1.9, 0.4-8.8) and extra bronchodilator use (2.2, 0.3-15). Self-reported ETS exposure was found to correlate significantly ($p<0.001$) with measured nicotine level, but the authors did not analyse it in relation to the risk of respiratory symptoms or bronchodilator use. The discussion and conclusions of the paper were more concerned with the usefulness and validity of the passive badge monitor than with drawing inferences about effects of ETS on health.

	Effect[1] (95% CI) in relation to four indices of ETS exposure			
Outcome	Any ETS	1-2 hrs ETS	3+ hrs ETS	Irritation
Severity	+0.6 (-0.1 to +1.4)	+0.1 (-3.0 to +2.9)	**+1.5 (+0.4 to +2.6)**	**+0.4 (-0.5 to +1.4)**
Physical health status	-2.0 (-4.4 to +0.5)	-0.1 (-3.0 to +2.9)	**-4.9 (-8.4 to –1.3)**	**-4.0 (-7.0 to -1.0)**
Asthma-specific quality of life[2]	+2.8 (-0.4 to +6.0)	+1.7 (-2.1 to +5.5)	+4.4 (-0.2 to +9.0)	**+5.0 (+1.2 to +8.9)**
Emergency dept. visits	**2.8 (1.2 to 6.4)**	2.5 (0.9 to 6.6)	**3.4 (1.1 to 10.3)**	**2.7 (1.1 to 6.6)**
Hospital admissions	**6.6 (1.3 to 33)**	4.6 (0.7 to 40)	**12.2 (1.5 to 102)**	2.4 (0.4 to 13.1)

[1] Difference in continuous score for first 3 outcomes, odds ratios for last 2.

[2] Higher scores are associated with poorer quality of life.

Significant differences are shown in bold.

The final publication (Eisner et al., 2002), described some further results from the study. While the 1998 paper (Eisner et al., 1998) concerned 451 non-smoking adults and related changes in regular ETS exposure over the 18 month period to corresponding changes in asthma outcome, the 2002 paper concerned 326 non-smoking adults and related any ETS exposure (home, work or other locations) at baseline to asthma outcomes at follow-up after adjustment for baseline severity of asthma score, age, sex, income and education attainment. Results were presented for five asthma outcomes and for four indices of ETS exposure (any

in last 7 days, 1-2 hrs in last 7 days, 3+ hrs in last 7 days or any eye or nose irritation), in each case with the comparison group being no ETS exposure. As shown above, quite a large number of significant associations were found, all in the direction of worse outcomes in the ETS-exposed group. The associations were not materially affected by further adjustment for gas stove or wood smoke exposure.

The Denver Study

A study in Denver, USA (Ostro et al., 1994) concerned 164 non-smoking asthmatic adults aged 18-70 (mean age 45.5 years), with 32.2% male. The study investigated the relationships between various indoor combustion products (including ETS) and daily symptoms. Both symptom and exposure data were recorded by the study participants over a 3-month period. Relative risks (95% CI) for ETS exposure (based on answers to the question "Were you exposed to cigarette smoke at home today?") for the various endpoints studied were as follows. The first relative risk, RR1, takes no account of autocorrelation between the repeated measures while the second, RR2, does.

Endpoint	RR1 (95% CI)	RR2 (95% CI)
Moderate or severe cough	1.21 (1.01-1.48)	1.15 (0.97-1.36)
Moderate or severe shortness of breath	1.85 (1.57-2.18)	1.34 (0.84-2.15)
Nocturnal asthma	1.24 (1.00-1.53)	1.08 (0.72-1.56)
Restricted activity	2.08 (1.63-2.64)	1.61 (1.08-2.46)

It can be seen that only for restricted activity did the association with ETS remain significant after adjustment (as is appropriate) for autocorrelation. Reporting the presence of smokers in the home at the start of the study was also associated with a significantly increased relative risk of 2.05 (95% CI 1.78-2.40) for moderate or severe shortness of breath. The authors noted that all the regressions adjusted for outdoor air pollution, the number of the day of the survey, and whether the subject reported a symptom on the previous day. Temperature, humidity and the age of the participants were considered as potential confounding variables, but were excluded from the final model. Relative risks for the four endpoints (RR1s) were presented separately for those with or without respiratory infections on that day. Associations with cough or wheeze seemed to be similar in the two subgroups, but associations with shortness of breath seemed stronger in those without respiratory infection.

The Portland Study

A study based on health maintenance organization members in Portland, USA (Sippel et al., 1999) concerned 619 adult subjects with asthma, including 548 non-smokers who were of mean age 38, with 43% male. The analyses related quality of life and hospital-based care both to smoking and to ETS exposure at home or at work. Most of the ETS analyses were unrestricted by smoking status and will not be summarized here. However, the results of one longitudinal analysis restricted to non-smokers were reported. This found that, after adjusting for age, gender, disease severity, diagnosis of COPD and non-asthma medication use, subjects who reported ETS exposure at baseline had more frequent episodes of hospital-based asthma care over the next 30 months than did those who reported no ETS exposure, with a relative risk of 2.87 (95% CI 2.15-3.82).

NHANES III

Using data from the Third *N*ational *H*ealth *a*nd *N*utrition *E*xamination *S*urvey (NHANES III), which was conducted between 1988 and 1994 in the USA, analyses were conducted relating pulmonary function to ETS exposure, as estimated by serum cotinine, among 440 non-smoking adults with current asthma (Eisner, 2002b). The adults were of mean age 42, with 44% male. Comparisons were made of subjects in the medium (>0.093 to 3.16 ng/ml) and high (>3.16 to <14 ng/ml) cotinine group with that in the low cotinine group (≤0.093 ng/ml), with adjustment for age, sex, height, education, income, previous smoking and race/ethnicity. Analyses were conducted of FEV_1, FVC and FEV_1/FVC ratio separately for each sex. As shown in the table below, which presents changes in the mean residual value (with 95% CI), statistically significant ($p<0.05$) differences noted were an increase in FEV_1 for medium cotinine in males, a decrease in FEV_1/FVC for high cotinine in males and a decrease in FEV_1 for high cotinine in females. Based on these results, the near significant decrease in FVC for high cotinine in females, and results for the whole population (including non-asthmatics), the authors concluded that *"ETS exposure is associated with decreased pulmonary function in adult females, especially those with asthma."* The authors also presented the results of further analyses using spirometric reference values derived for never smokers with no respiratory symptoms or conditions. Here only the decrease in FEV_1 for high cotinine in females remained statistically significant.

	Changes in mean residual spirometric values (95% CI) compared to low[1] cotinine group	
Sex/endpoint	Medium cotinine[1]	High cotinine[1]
Males		
FEV_1 (ml)	+569 (+78 to +1060)	+242 (-169 to +653)
FVC (ml)	+222 (-92 to +536)	-30 (-331 to +271)
FEV_1/FVC (%)	-0.54 (-1.8 to +0.73)	-1.6 (-2.8 to -0.30)
Females		
FEV_1 (ml)	-87 (-278 to +104)	-261 (-492 to -30)
FVC (ml)	-63 (-278 to +152)	-291 (-601 to +20)
FEV_1/FVC (%)	-0.46 (-2.0 to +1.1)	-1.6 (-3.3 to 0.19)

[1] See text above for cotinine levels.

4.1.3. Summary of the Studies

Below we summarize some of the main features of the studies.

- *Design.* Two of the studies (Künzli et al., 2000; Eisner, 2002b) were of cross-sectional design in which ETS exposure was related to lung function in asthmatics identified by questionnaire. The remaining studies were of cases identified, usually at clinics, but in one study (Sippel et al., 1999) from insurance records. Most of these involved follow-up of these cases for varying period of time, though this was not so in two studies (Jindal et al., 1996; Jindal et al., 1999).
- *Size.* The largest number of asthmatics considered in any study was 548 in the Portland study (Sippel et al., 1999), and varied between 164 and 451 otherwise,

except for two studies each involving only 50 adults (Jindal et al., 1999; Eisner et al., 2001).

- *Sex and age.* Of the studies conducted in India, one was of women (Jindal et al., 1999) with the sex distribution not reported in the other two (Jindal et al., 1994; Jindal et al., 1996). The other studies all involved both sexes, with men forming between 28% and 44% of the sample, reflecting the known higher frequency of adult asthma in women.

  Where the average age of the sample was known it was typically around 40, except for the third study in India (Jindal et al., 1999), which involved women aged between 20 and 40.
- *Restriction to non-smokers.* Of the eight studies considered, only two were clearly restricted to lifelong never smokers (Jindal et al., 1994; Künzli et al., 2000). The studies in northern California (Eisner et al., 1998; Eisner et al., 2001; Eisner et al., 2002) and Portland (Sippel et al., 1999) and the one based on NHANES III (Eisner, 2002b) clearly included ex-smokers together with never smokers in their analyses. Two studies (Ostro et al., 1994; Jindal et al., 1996) ambiguously referred to being of *"nonsmokers,"* while one (Jindal et al., 1999) merely considered that *"most women were likely to be non-smokers."*
- *Source of ETS information.* In most of the studies ETS exposure (from the spouse, at home, and/or at work) was obtained from questionnaires, but in two studies objective measures were used, one based on nicotine from a personal nicotine badge monitor (Eisner et al., 2001), the other based on serum cotinine (Eisner, 2002b). No study in adults recorded ETS exposure in childhood, or maternal smoking in pregnancy.
- *Potential confounding variables.* The three studies in India (Jindal et al., 1994; Jindal et al., 1996; Jindal et al., 1999) and one of the analyses of the northern California study (Eisner et al., 2001) took no potential confounding variables at all into account, not even age or sex. The remaining publications took into account differing factors including outdoor air pollution, survey day and previous symptoms (Ostro et al., 1994); age, sex, race and income and also baseline severity for follow-up analyses (Eisner et al., 1998); age, sex, severity of asthma, diagnosis of COPD and non-asthma medication (Sippel et al., 1999); age, height, ETS at home, occupational gas/dust/smoke and area of residence (Künzli et al., 2000); age, sex, height, education, income, previous smoking, race/ethnicity (Eisner, 2002b); and age, sex, income, education, baseline asthma severity (Eisner et al., 2002).
- *Other issues.* One of the studies in India (Jindal et al., 1996) was reported only as an abstract, while the other two (Jindal et al., 1994; Jindal et al., 1999) included major statistical errors in their analyses.

4.2. RESULTS

4.2.1. Asthma Exacerbation and Severity

Table 4.1 summarizes results from eight publications relating to a variety of endpoints for asthma exacerbation and severity. The endpoints can be broadly classified into groups:

Acute exacerbations. These include such endpoints as emergency department visits, hospitalisations, acute episodes and restricted activity days. All but one of the publications (Eisner et al., 2001) reported data here. Significant associations are evident in four studies (Ostro et al., 1994; Jindal et al., 1996; Sippel et al., 1999; Eisner et al., 2002) and are not seen in one (Jindal et al., 1999). In one study (Jindal et al., 1994), some significant associations might have been demonstrated, but this is unclear due to doubts about adequacy of the statistical analysis. In the study in Northern California (Eisner et al., 1998), the data appeared conflicting, with incidence of acute exacerbations higher in those with ETS exposure at baseline and reduced in those who quit, but not increased in those who started exposure or in those who had continuing exposure at baseline and during the follow-up period.

Severity and symptoms. An association with symptoms was reported in one study (Eisner et al., 2001) but not in another (Ostro et al., 1994). Analyses based on the northern California study reported results for an index of severity. In both publications (Eisner et al., 1998; Eisner et al., 2002), some ETS variables showed a significant association with severity, and some did not. As noted above for exacerbations, there was an increase associated with ETS exposure at baseline and a decrease associated with quitting, but no increase in those who started ETS exposure after baseline or who had continuing exposure at baseline and during the follow-up period.

Drug use. Bronchodilator use was strongly related to nicotine level as determined by personal monitor in one study (Eisner et al., 2001) but was not significantly related to smoking by the husband in another (Jindal et al., 1999). Reported significant associations of ETS with use of bronchodilators and steroids in one study (Jindal et al., 1994) are not statistically reliable.

Quality of life and general health. This was only considered in the northern California study. AQOL was generally worse in relation to ETS exposure in the later publication (Eisner et al., 2002), although differences were not always significant for every exposure index. In the earlier publication (Eisner et al., 1998), it was worse in those ETS exposed at baseline, but did not change on stopping or starting exposure and was not significantly worse in those who continued to be exposed. Results for two components of a general health index, a physical health score and a mental health score, were also provided. These do not relate so directly to asthma exacerbation. No association was seen between ETS exposure and the mental health score, but some analyses showed a significantly reduced physical health score associated with ETS exposure (or a significant improvement following quitting).

Associations of ETS exposure with severity and symptoms, with drug use, and with quality of life and general health, have not clearly been shown, the data being rather limited for each group of endpoints. The data for acute exacerbations are much more suggestive of an association.

Table 4.1. Summary of results for adults relating asthma exacerbation and severity to ETS exposure

Publication	Endpoint	Results by ETS exposure		
Jindal et al., 1994		*Unexposed to ETS at home and work*	*Exposed to ETS at home or work*	*OR (95% CI)*[1]
	Occurrence in last year of:			
	Emergency department visit	52/100 (52%)	60/100 (60%)	1.38 (0.79-2.42)
	Hospitalisation	30/100 (30%)	30/100 (30%)	1.00 (0.55-1.83)
	Acute episodes	58/100 (58%)	62/100 (62%)	1.18 (0.67-2.08)
	Absence from work due to asthma (>2 wks)	60/100 (60%)	66/100 (66%)	1.29 (0.73-2.30)
	Parenteral drugs required	64/100 (64%)	64/100 (64%)	1.00 (0.56-1.78)
	Daily bronchodilators[2]	56/100 (56%)	66/100 (66%)	1.53 (0.86-2.70)
	Intermittent steroids	42/100 (42%)	56/100 (56%)	1.76 (1.00-3.08)
	Complications	6/100 (6%)	8/100 (8%)	1.36 (0.45-4.08)
	Mean per patient per year of:			*p*[3]
	Emergency department visits, n	0.60	0.82	<0.01
	Hospitalisations, n	0.33	0.34	NS
	Acute episodes, n	0.60	1.32	<0.01
	Parenteral bronchodilator injections, n	6.0	8.6	<0.01
	Absence from work due to asthma, wks	3.0	3.6	<0.01
	Steroid requirement, wks	8.6	11.3	<0.01
	Bronchodilator required, wks	36.3	38.3	NS
Ostro et al., 1994				*OR (95% CI)*[4] *for at home ETS*
	Moderate or severe cough			1.15 (0.97-1.36)
	Moderate or severe shortness of breath			1.34 (0.84-2.15)
	Nocturnal asthma			1.08 (0.72-1.56)
	Restricted activity			1.61 (1.08-2.46)
Jindal et al., 1996	Acute vs non-acute asthma			ETS exposure higher in acute patients (p<0.01)

Eisner et al., 1998		OR (95% CI) for specified ETS exposure			
		ETS at baseline vs no ETS	*ETS stopped vs ETS continued*	*ETS started vs no ETS*	*ETS continued vs no ETS*
	Emergency department visit	2.1 (1.2-3.5)	0.4 (0.2-0.97)	0.9 (0.4-1.8)	NS
	Urgent physician visit	1.9 (1.1-3.3)	0.6 (0.3-1.4)	1.0 (0.5-2.0)	NS
	Hospitalisation for asthma	1.9 (1.02-3.6)	0.2 (0.04-0.97)	0.6 (0.2-1.9)	NS
	Restricted activity	–[5]	0.8 (0.4-1.7)	NS	NS
		Direction of association (p-value)			
		ETS at baseline vs no ETS	*ETS stopped vs no ETS*	*ETS started vs no ETS*	*ETS continued vs no ETS*
	Asthma severity score	Greater (p=0.03)	Improved (p<0.001)	NS	NS
	Quality of life	Worse (p=0.04)	NS	NS	NS
	Mental score	NS	NS	NS	NS
	Physical score	Worse (p=0.04)	Improved (p=0.05)	NS	NS
Jindal et al., 1999		*Husband non-smoker*	*Husband smokes*	*OR (95% CI)*	
	Continuous bronchodilator therapy required	7/27 (26%)	9/23 (39%)	1.84 (0.55-6.10)	
				Significance	
	Acute episodes in year	4.00	4.83	NS	
Sippel et al., 1999		*Unexposed at home and work*	*Exposed to ETS at home or work*	*RR (95% CI)*	
	Hospitalisations	89/878 person-years	148/528 person-years	2.87 (2.15-3.82)	
Eisner et al., 2001		OR (95% CI) by level of nicotine ($\mu g/m^3$)			
		None	*>0-0.05*	*≥0.05*	*Trend p*
	Respiratory symptoms	1.0	1.9 (0.4-8.8)	6.8 (1.4-32.3)	0.017
	Extra bronchodilator use	1.0	2.2 (0.3-15.0)	8.1 (1.3-50.0)	0.022

Table 4.1. Continued

Publication	Endpoint	Results by ETS exposure			
Eisner et al., 2002		OR (95% CI) for specified ETS exposure			
		Any ETS vs none	*<1-2 hrs/wk vs none*	*3+ hrs/wk vs none*	*ETS irritation vs none*
	Emergency department visit	2.8 (1.2-6.4)	2.5 (0.9-6.6)	3.4 (1.1-10.3)	2.7 (1.1-6.6)
	Hospitalisation	6.6 (1.3-33)	4.6 (0.7-40)	12.2 (1.5-102)	2.4 (0.4-13.1)
		Difference in continuous scores (95% CI)			
		Any ETS vs none	*<1-2 hrs/wk vs none*	*3+ hrs/wk vs none*	*ETS irritation vs none*
	Severity	+0.6 (-0.1 to +1.4)	+0.1 (-3.0 to +2.9)	+1.5 (+0.4 to +2.6)	+0.4 (-0.5 to +1.4)
	Physical health status	-2.0 (-4.4 to +0.5)	-0.1 (-3.0 to +2.9)	-4.9 (-8.4 to –1.3)	-4.0 (-7.0 to –1.0)
	Asthma-specific QOL[6]	+2.8 (-0.4 to +6.0)	+1.7 (-2.1 to +5.5)	+4.4 (-0.2 to +9.0)	+5.0 (+1.2 to +8.9)

NS = not significant ($p \geq 0.05$)

[1] Calculated by us from data presented. The authors claimed significance at $p<0.01$ for bronchodilators and for intermittent steroids, but this seems inconsistent with the data given.

[2] Results are also given for intermittent bronchodilators, but the percentages given (42% and 56%) seem inconsistent with the results for daily bronchodilators, particularly for the exposed group where the percentage given is 66% and 56% plus 66% = 122%.

[3] The significances were as presented by the authors, and may well be erroneous, although they cannot be checked.

[4] Results used are with correction for autocorrelation and repeated measures.

[5] Results for restricted activity were only presented after baseline.

[6] Higher scores are associated with poorer quality of life.

Table 4.2. Summary of results for adults relating lung function to ETS exposure

Publication	Exposure	Lung function variable			
		FEV_1	FVC	FEV_1/FVC	$FEF_{25-75\%}$
Jindal et al., 1994	No ETS exposure	80.8%	90.9%	78.4%	75.7%
	ETS at home or work	68.7%	89.4%	63.5%	54.3%
	Significance[1]	p<0.05	NS	p<0.05	p<0.05
Jindal et al., 1999	Husband does not smoke	79.4%		86.3%	
	Husband smokes	77.9%		83.6%	
	Significance[2]	NS		NS	
Künzli et al., 2000	Difference in lung function associated with ETS exposure at work (95% CI)				
	All subjects	-4.8% (-9.2 to +0.0)	-1.7% (-5.5 to +2.1)		-12.4% (-20.4 to -3.7)
	Male	+0.5% (-7.9 to +9.6)	+1.4% (-4.0 to +7.1)		-1.4% (-18.0 to +18.5)
	Female	-8.7% (-14.5 to –2.5)	-4.4% (-9.6 to +1.1)		-20.8% (-32.0 to -7.6)
Eisner, 2002b	Change in mean residual lung function values (95% CI) compared to low cotinine group[3]				
	Male:				
	Medium cotinine	+569 ml (+78 to +1060)	+222 ml (-92 to +536)	-0.54% (-1.8 to +0.73)	
	High cotinine	+242 ml (-169 to +653)	-30 ml (-331 to +271)	-1.6% (-2.8 to -0.30)	
	Female:				
	Medium cotinine	-87 ml (-278 to +104)	-63 ml (-278 to +152)	-0.46% (-2.0 to +1.1)	
	High cotinine	-261 ml (-492 to -30)	-291 ml (-601 to +20)	-1.6% (-3.3 to +0.19)	

[1] Significance as reported by the author. See section 4.1.2 for a discussion of statistical errors in this study.

[2] Significance calculated by us.

[3] Serum cotinine groups are “low” to 0.093 ng/ml, “medium” >0.093 to 3.16 ng/ml and “high” >3.16 to 14 ng/ml.

4.2.2. Lung Function

Table 4.2 summarizes lung function results from the four studies providing relevant data for asthmatic adults.

The results for FEV_1 are rather conflicting. ETS was associated with a significant decline in FEV in one study in India (Jindal et al., 1994) and in females in the Swiss study (Künzli et al., 2000), and high cotinine was associated with a significant decline in females in a US study (Eisner, 2002b). However, no association was evident in another study in India (Jindal et al., 1999) or in males in the Swiss study (Künzli et al., 2000), and FEV_1 was positively associated with cotinine in males in the US study (Eisner, 2002b).

None of the analyses for FVC show a significant association, with no clear evidence of any consistent relationship.

Three studies reported results for the FEV_1/FVC ratio. No association with ETS exposure was seen in one study (Jindal et al., 1999) or in the medium/low cotinine comparison in the US study (Eisner, 2002b). However, evidence of a reduction in the FEV_1/FVC ratio associated with ETS exposure was seen in another study (Jindal et al., 1994) and in the high/low cotinine comparisons in the US study (Eisner, 2002b), though here only the results for males were statistically significant.

$FEF_{25-75\%}$ was significantly reduced in association with ETS exposure in one study (Jindal et al., 1994) and in females, but not males, in another study (Künzli et al., 2000).

While the data shown in Table 4.2 give some support to the possibility that ETS exposure may be associated with reduced lung function, the findings are limited, and not always consistent. No firm conclusions can be drawn.

4.2.3. Bronchial Responsiveness

Only one study (Jindal et al., 1999) presented data for bronchial responsiveness. In this study PD_{20}, the dose of histamine to produce a 20% fall or greater in FEV_1 was noted to be significantly ($p<0.01$) lower if the husband smoked and to be significantly ($p<0.01$) related to an ETS exposure index based on the product of years and hours of exposure. Based on the data presented, we calculate that the first relationship is in fact not significant, and though we cannot check significance for the second, there must be doubt about it. In any event, the very limited data on bronchial responsiveness in adults cannot allow any conclusion to be reached.

4.3. Summary and Conclusions

4.3.1. Summary

Ten relevant publications, apparently relating to eight studies, were identified. Four of the studies were conducted in the USA, three in India and one in Switzerland. One study was of women aged 20-40, the other studies (where details were known) being of men and women of average age 40. Asthmatic women were generally commoner than asthmatic men. Only two studies were restricted to lifelong never smokers, the rest being of non-smokers.

Most studies were of cases identified from medical (or insurance) records, but two studies were of cross-sectional design with ETS exposure related to lung function in asthmatics identified by questionnaire. Two studies used a nicotine-based marker of ETS exposure, with other studies relying on questionnaire response. No study recorded ETS exposure in childhood or maternal smoking in pregnancy.

The four studies in the USA and the study in Switzerland took a range of potential confounding variables into account in at least some of their analyses. The three studies in India took no potential confounding variables at all into account, not even age or sex. One of these three studies was reported only as an abstract, while the other two included major errors in their statistical analyses.

Six of the eight studies reported results for acute exacerbations (including such endpoints as emergency department visits, hospitalisations, acute episodes and restricted activity days). All but one reported significant positive associations in at least one analysis. Data relating to other endpoints were more rarely studied and, though some associations were reported, more evidence is needed.

Data from four studies gave some support to the possibility that ETS exposure may be associated with reduced lung function, but the limited findings were not always consistent and no firm conclusions can be drawn.

One of the studies in India reported an association of ETS exposure with bronchial responsiveness, but the statistical analysis is open to question. Since no other study provided relevant data, conclusions cannot be drawn here.

4.3.2. Other Published Reviews of the Evidence

The California EPA report *"Health effects of exposure to environmental tobacco smoke"* (National Cancer Institute, 1999) contained a section on *"asthma (exacerbation),"* about half of which concerned the *"epidemiologic evidence."* The review of this evidence considered that the studies provide *"suggestive evidence that ETS exposure may exacerbate adult asthma."*

The epidemiological evidence published before 1999 relating ETS exposure to severity of asthma in adults was in fact extremely limited. This is also clear from two other reviews published at the end of the 1990s.

One of these, entitled *"Effects of environmental tobacco smoke exposure on pulmonary function and respiratory health in adults: update 1997"* (Witorsch, 1998) contained quite a detailed analysis of the experimental evidence on ETS exposure in asthmatics. As regards epidemiology, no actual attempt was made to separate out effects on asthmatics and the normal population and of the 18 studies cited *"of asthma incidence, exacerbation or symptoms,"* only one of the studies in adults we identified (Ostro et al., 1994) being referred to. The others were mainly studies of normal individuals, though some (e.g. Hong et al., 1994) are ones rejected by us, for reasons described in section 4.1.1.

The other review was entitled *"Environmental tobacco smoke exposure and asthma in adults"* (Weiss et al., 1999). Again this review gave greater attention to the more extensive experimental evidence. As regards the epidemiological evidence, it cited two studies we identified (Jindal et al., 1994; Ostro et al., 1994). It regarded the data from the study in India as providing *"positive findings"* which *"need cautious interpretation"* because of potential

bias in selection, recall and exposure assessment, failing to note the statistical errors described in section 4.1.2. For the Denver study (Ostro et al., 1994) the authors surprisingly cited only the results of those analyses that did not take into account the repeated measures design, so giving a false impression of significance of the associations. Overall, taking the experimental and epidemiological evidence into account (also including studies of asthma induction) they concluded that *"It appears that there are only scant data assessing the role for ETS exposure in adult asthma"* and that *"ETS exposure has not yet been confirmed as a hazard for adults with asthma."*

A review entitled *"Environmental tobacco smoke and adult asthma"* (Eisner & Blanc, 2000) concluded that *"Among adults with pre-existing asthma, ETS appears causally related to adverse health outcomes."* In the section on *"ETS exposure and exacerbation of pre-existing adult asthma"* four studies are cited, one of which (Blanc et al., 1999) did not actually report any results restricted to asthmatics. Only three relevant studies were cited (Jindal et al., 1994; Ostro et al., 1994; Sippel et al., 1999). As in the previous review (Weiss et al., 1999), the authors incorrectly only report the results unadjusted for repeated measures from the Denver study (Ostro et al., 1994). As the authors point to weaknesses in the study in Chandigarh (Jindal et al., 1994), it seems doubtful if their conclusions were justified based on the evidence they considered, especially when they regard the evidence from the chamber studies as *"limited by small sample size, variable subject inclusion criteria and variation in chamber exposure methodology"* and only suggesting *"a modest adverse effect of acute ETS exposure on pulmonary function."*

A further review published that year, on *"Environmental tobacco smoke and respiratory diseases"* (Jaakkola, 2000) was broad ranging. In the summary of the paper the author stated that *"A limited number of studies on ETS and asthma in adults suggest that ETS exposure increases the risk of asthma and contributes to poor overall control of asthma."*

A brief review on *"Cigarette smoking and asthma"* (Ulrik & Lange, 2001) included a section on *"Environmental smoke exposure and asthma"* and stated that *"From the available evidence, it can be concluded that exposure to environmental tobacco smoke leads to worse asthma control, including a lower level of lung function and more severe exacerbations, in both children and adults with asthma."* However, there was no discussion of study weaknesses, and only three studies of asthma exacerbation in adults were considered (Jindal et al., 1994; Eisner et al., 1998; Sippel et al., 1999).

A review entitled *"Environmental tobacco smoke and adult asthma"* (Eisner, 2002a) included a section *"Environmental tobacco smoke exposure and exacerbation of pre-existing adult asthma,"* and concluded that *"the evidence suggests a causal relationship between ETS exposure and … asthma exacerbation among adults."* This was an update of an earlier review (Eisner & Blanc, 2000). Of the studies cited, two (Mannino et al., 1997; Blanc et al., 1999) did not actually report any results limited to asthmatics, and for another (Ostro et al., 1994) inappropriate results are cited (see comments on Weiss et al., 1999 above). For the other studies cited (Jindal et al., 1994; Sippel et al., 1999; Künzli et al., 2000; Eisner et al., 2001; Eisner, 2002b), all considered earlier in this section, the results are briefly described, but no study-specific limitations are noted.

A second review published in 2002, entitled *"Effects of environmental tobacco smoke on the respiratory health of adults"* (Jaakkola & Jaakkola, 2002) concluded that *"There is limited evidence indicating an increased risk of its [ETS] causing asthma … and for poor control of established asthma."* Only eight published studies were cited. Four we consider

relevant (Jindal et al., 1994; Ostro et al., 1994; Jindal et al., 1999; Sippel et al., 1999), and four (Dales et al., 1992; Abramson et al., 1995; Blanc et al., 1999; Tarlo et al., 2000) we reject for reasons discussed in section 4.1.1. Reference was also made to a later published study (Eisner, 2002b) as a personal communication. As with the review considered in the previous paragraph, the data cited from the Denver study (Ostro et al., 1994) seem inappropriate.

In their *"Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant"* (California Environmental Protection Agency [EPA], 2005), the California EPA included *"asthma induction and exacerbation in children and adults"* in their list of *"Effects Causally Associated with ETS Exposure."* The coverage was quite complete, the California EPA missing only two studies we consider (Jindal et al., 1996; Eisner et al., 2002). However, there was no attempt to bring together results for specific types of endpoints and no discussion of study weaknesses. The report concluded that *"Taken together, the evidence is consistent with a causal effect of ETS on adult asthma exacerbation."* This is not in conflict with our own conclusions, expressed below.

4.3.3. Conclusions

The epidemiological studies in adult asthmatics are quite limited. However, they suggest strongly that ETS exposure increases the risk of acute exacerbations. An effect on reduced lung function may also exist, but has not been clearly demonstrated.

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Chapter 5

EXACERBATION OF ASTHMA – EPIDEMIOLOGICAL EVIDENCE IN CHILDREN

5.1. THE STUDIES

5.1.1. Introduction

The literature searches identified 60 publications which together described the results of a total of 47 relevant epidemiological studies in children. 18 of the studies were conducted in the USA, four in Canada, 13 in Europe (in a total of 10 countries), five in Turkey or the Middle East, three in India or the Far East, three in Africa and one in New Zealand. Seven references were published as abstracts.

A further 17 publications described studies that seemed possibly relevant, but did not meet the inclusion criteria. The reasons for rejection included no actual data collected on ETS exposure, the study only reporting on whether tobacco smoke brought on wheezing (Speer, 1968), no results reported relating ETS exposure to aggravation of asthma (Wood et al., 1993; Huss et al., 1994; Chadwick, 1996; Gilliland et al., 2001; Morgan et al., 2004), results not reported separately for children (Tarlo et al., 2000; Bayona et al., 2002), results not reported separately for asthmatics (Lebowitz, 1984a; Lebowitz, 1984b; Toyoshima et al., 1987; Strachan et al., 1990; Agudo et al., 1994; Henderson et al., 1995; Fielder et al., 1999; Willers et al., 2000) and endpoint (respiratory illness) too broad (Gilliland et al., 2003). A further study (Bener et al., 1991) was rejected as the data presented seemed totally implausible, with 85% of a sample of schoolchildren reported to have asthma and the odds of having a frequent attack 34 times higher if one of the parents smoked.

The studies are described individually in sections 5.1.2 (USA), 5.1.3 (Canada), 5.1.4 (Europe), 5.1.5 (Asia) and 5.1.6 (Other). Section 5.1.7 then summarizes various relevant aspects of the studies considered and section 5.2 brings together the findings by type of endpoint.

5.1.2. Description of the Studies – USA

The Minnesota Study

O'Connell & Logan (1974) collected information from 400 asthmatic children aged 2 to 16 years (60% male) on whether smoking induced or aggravated their asthma. For 37 children whose parents' smoking was considered to have a significantly adverse effect on their asthma, it was recommended as a part of treatment that this exposure be eliminated, and 35 were available for follow-up six months to two years later. By then, the asthma had improved in 90% (18/20) of children where parents had stopped smoking and in 27% (4/15) where parents had continued. The relative risk can be estimated as 3.38 (1.44-7.91). Results on whether smoking irritated the respiratory tract were also presented for 228 children without asthma, allergic rhinitis or atopic dermatitis and whose siblings had no allergic disease. This study has some weaknesses. It uses endpoints which are rather soft and poorly defined, and it is hard to tell whether responses relate to tobacco smoke in general or to the parents' smoking. No statistical tests were conducted, though, as shown above, differences by stopping smoking are statistically significant.

The Michigan and Massachusetts Study

In random population surveys of children aged 0-17 conducted in an urban county in Michigan and a rural county in Massachusetts, USA, Gortmaker et al (1982) collected data on the prevalence of asthma and of functionally impairing asthma and on parental smoking, but not on smoking by the child. Although the paper is mainly concerned with prediction of asthma and of function-impairing asthma by various factors including parental smoking, these analyses are not relevant to exacerbation of asthma. However data were provided which allow one to relate maternal smoking to the probability, among asthmatic children, of the asthma being functionally impairing. This analysis, summarized below, shows a non-significant tendency for the probability to be higher if the mother smokes.

Sample	Functional impairment	Mother non-smoker	Mother smoker	OR (95% CI)
Michigan	No	71	69	
	Yes	20	28	1.44 (0.74-2.79)
Massachusetts	No	11	11	
	Yes	3	4	1.33 (0.24-7.40)
Total (adjusted for sample)	No	82	80	
	Yes	23	32	1.43 (0.79-2.65)

The First New York Study

Evans et al. (1987) studied 276 asthmatic children from low income families, collecting data on smoking by the parents (and by the children themselves), on pulmonary function (at a random clinic visit up to 1 year after interview), on emergency health care use in the year prior to the interview and on various other potential confounding variables. The children were of average age 9.9 years, with 60% male. After eliminating 77 with some data missing and 8 who reported being smokers, the analyses carried out involved 191 children. Compared to children with no smokers in the household, there was no evidence of a significant reduction in pulmonary function in children in households where one or more parents smoked. Indeed

mean pulmonary function scores were somewhat higher where a smoker was present (FEV_1 1.60ℓ vs 1.49ℓ; PEFR 3.19ℓ/sec vs 2.74ℓ/sec; $FEF_{25-75\%}$ 1.60ℓ/sec vs 1.42ℓ/sec). There was also no significant association of household smoking with the mean number of hospitalisations in the year prior to enrolment. Household smoking was, however, significantly associated with an increase in the mean frequency of visits to the emergency room over the last year. The difference was significant whether or not adjustment for the mean number of days with asthma symptoms per month was made (3.46 vs 2.12, p=0.008) or was not made (3.09 vs 1.83, $p<0.05$). Frequency of asthma symptoms was not itself associated with household smoking. The strength of the association of household smoking with emergency room visits was unaffected by counting only households with 2 or more smokers as exposed. It is unclear how parental smoking might markedly increase the frequency of emergency room visits without apparently worsening lung function, or increasing symptom prevalence or the frequency of hospitalisation.

The Boston Study

O'Connor et al. (1987) studied the relationship between parental smoking and airway reactivity in 286 children, including 21 asthmatics (mean age 12 years, 62% male) none of whom smoked themselves. Nine had a mother who smoked. Compared to the other 12 asthmatics, those with a smoking mother had a lower mean FEV_1 (100.8% vs 102.9%) and $FEF_{25-75\%}$ (76.1% vs 85.8%) and a higher mean FVC (107.8% vs 104.0%) as a percentage of predicted, none of these differences being statistically significant. Following cold air challenge, the response (fall in FEV_1 following challenge expressed as a percentage of predicted FEV_1) was almost significantly higher when the mother smoked (24.0 vs 11.9, p=0.07). Using linear regression to adjust for predicted FEV_1 this difference became significant (p=0.02). Adjustment for other independent variables in a multiple regression analysis did not affect this conclusion. Paternal smoking was unrelated to bronchial responsiveness to cold air. The small sample size and the marginal nature of the significance reported limit interpretation of these findings.

The Second New York Study

In an abstract Lilienfeld et al. (1990) briefly described results of a study of inner city children aged 3-14 years, comparing 72 acute asthmatics in a hospital emergency room and 35 non-acute asthmatics attending an asthma clinic. Urinary cotinine/creatinine ratio (CCR) was used as an index of ETS exposure, the acute asthmatics having a non-significantly lower frequency of a ratio greater than 30 ng/mg (OR 0.92, p=0.85). Household smoking was also determined by questionnaire but results comparing these two groups were not given in the abstract. The authors concluded that *"recent smoke exposure is not the trigger of the acute attack."*

The results were later described more fully (Ehrlich et al., 1992). The groups of acute and non-acute asthmatics were reported to be of similar age (range 3-14 years), sex (62% male) and socio-economic status (SES), all the children being non-smokers. African-American children were somewhat over-represented in the acute group (37% vs 26%), but not significantly. The acute asthmatics were significantly more likely to have had a recent upper respiratory infection (URI) (OR 2.5, 95% CI 1.1-5.6), and to have previously used the emergency room (97% vs 86%, p=0.02). Interestingly they were less likely to have previously

attended an asthma clinic (65% vs 100%, p<0.001), or use daily asthma medication (36% vs 80%, p<0.001). As shown below, the groups did not differ on ETS exposure variables.

The authors noted that *"we were unable to show an effect of passive smoke exposure on the precipitation of acute asthmatic effects."*

	Asthma		
ETS exposure variable	Acute	Non-Acute	OR (95% CI)
Any smoker at home	53%	57%	0.84 (0.37-1.89)
Cigs/day by all smokers	7.7	10.7	Not significant
Maternal caregiver smokes	40%	51%	0.64 (0.28-1.44)
CCR1 ≥ 30 ng/mg	38%	39%	0.90 (0.39-2.06)
Mean CCR (ng/mg)	46.2	38.5	Not significant
Number of subjects	72	35	

[1] CCR = cotinine/creatinine ratio.

National Health Interview Survey

In an analysis based on 4331 children aged 0-5 years participating in the 1981 US National Health Interview Survey, Weitzman et al. (1990b) presented a table giving, by maternal smoking status in pregnancy, the number of mothers, the prevalence of asthma and the percentage of children using asthma medications. These data can be used to estimate ORs for asthma medication by amount of maternal smoking in pregnancy among asthmatics.

	Maternal smoking in pregnancy (cigs/day)				
	0	1-9	10+	Any	Total
With asthma	74	17	26	43	117
Using asthma medications (%)	16 (21.6)	3 (17.6)	11 (42.3)	14 (32.6)	30 (25.6)
OR	1.00	0.78	2.66	1.75	
(95% CI)		(0.20-3.04)	(1.02-6.91)	(0.75-4.07)	

These results, which are unadjusted for any potential confounding factor, show some evidence of an association, which is marginally significant (p<0.05) for maternal smoking of 10+ cigs/day.

A figure was also presented showing mean number of overnight hospitalisations by maternal smoking in pregnancy, separately for non-asthmatic and asthmatic children. For asthmatic children, the numbers (1.1 for no smoking, 1.3 for 1-9/day and 1.0 for 10+/day) showed no significant relationship.

In a further paper by the same group (Weitzman et al., 1990a) data were presented for children aged 2-5 years on the basis that parents of younger children might mistakenly report respiratory illnesses associated with wheezing as asthma. The following table can be constructed:

	Maternal smoking in pregnancy (cigs/day)	
	None or 1-9	10+
With asthma	76	23
Using asthma medication (%)	14 (18%)	9 (39%)
OR (95% CI)	1.00	2.85 (1.03-7.88)

These data considerably overlap those tabulated previously.

The Portland Study

Chilmonczyk et al. (1993), and previously in an abstract Salmun et al. (1992), reported data for 199 asthmatic children aged up to 13 (72% boys) on smoking by parents and other household members, smoking at day-care, cotinine in urine, number of acute exacerbations of asthma in the past 12 months, lung function (from 145 of the children), serum theophylline (from 63 of the children) and on demographic and other variables. The main finding was a trend towards an increasing number of exacerbations of asthma and decreasing lung function with increasing ETS exposure, whether based on parental reports (no exposure, mother or others smoke, mother and others smoke) or on urinary cotinine adjusted for creatinine (<10, 10-39, >39 ng/mg). The increased risk of asthma exacerbations was significant after adjustment for maternal age and education level, and for the child's age, sex and day-care attendance, with children in the highest exposure group having almost twice the number of exacerbations of the lowest exposure group (change per category of reported exposure 0.83, 95% CI 0.39 to 1.26, and per category of CCR 0.63, 95% CI 0.10 to 1.07). Although the corresponding reductions in FEV_1 were not statistically significant, significant reductions were seen in FEV_1/FVC and $FEF_{25-75\%}$ for both exposure indices. In children prescribed theophylline, serum theophylline levels were similar in those exposed and unexposed to smoke in the home, suggesting that the two groups followed medical advice similarly.

The authors emphasized the value of urinary cotinine as a marker of ETS exposure, and concluded that their study *"provides further evidence of an association between exposure to environmental tobacco smoke and pulmonary morbidity in children with asthma."* Although data were collected on severity of the underlying disease, no account was made of this in analysis. Did the more ETS exposed children have more attacks because they were exposed more, or because they had more severe disease to start with?

The Baltimore Study

Ogborn et al. (1994) collected urine samples and data on parent-reported ETS exposure from 56 children aged 3-11 (57% male) on two occasions, first when they attended the hospital emergency department during an acute episode of asthma and second 3 to 4 weeks later when free of symptoms of asthma and feeling well. Using matched-pairs analysis no significant difference was seen between the acute and the well visit in urinary cotinine (means 81 vs 77 ng/ml), CCR (93 vs 97 ng/ml) or the proportion with a ratio of 30 ng/ml or above (80% vs 82%). There was also no significant difference in the reported hours of exposure in the past 48 hours (mean 32 vs 32 hours) or the total number of cigarettes smoked at home in the past 24 hours (31 vs 25). There was, however, a significant (p=0.02) difference in the amount of exposure:

	Amount of ETS exposure			
	None	A little	Some	A lot
Acutely asthmatic	10	12	16	14
Well	17	13	20	4

The authors believed that *"this difference may have been due to the parent becoming more sensitised to the issue of passive smoke exposure by the study questionnaire itself and perhaps wanting to minimize the reported exposure."* It also seems possible that knowledge of the asthmatic attack may have affected the answers given to this rather subjective question.

The Seattle Study

In a study first reported as an abstract, Abulhosn et al. (1995) followed up 22 children aged 2-9 years who had been hospitalised for asthma. 11 children living in homes where 1 or more parents smoked and 11 living in non-smoking homes were compared. The groups were stated to be *"comparable"* in age, gender and pre-admission National Institutes of Health (NIH) chronic asthma severity score. They were also similar regarding the proportion discharged home on anti-inflammatory and on beta-agonist asthma therapy. Based on data reported by the parents over the four weeks following hospital discharge, the children in smoking homes had more symptomatic days (3.3 vs 1.4, $p<0.05$). The reduction in use of beta-agonist therapy over the period following discharge was also less in these children (from 18.5 to 14.6 vs from 18.5 to 6.3 treatments per week, $p=0.001$). Children in smoking homes also had more symptomatic nights (2.3 vs 1.4) though this was not significant ($p>0.1$). The authors concluded *"that children returning to smoking households following hospitalisation for acute asthma remain more symptomatic despite greater beta-agonist therapy within four weeks after hospital discharge and therefore recover less completely when compared with those children returning to non-smoking homes."*

Two years later, a paper appeared (Abulhosn et al., 1997). Little extra relevant material was presented. It was noted that the 22 children were aged 2-13 (not 2-9 as previously stated), the mean age being 5.2 in both the groups of 11 children being compared. Nine of the children (41%) were boys. The difference in symptomatic days in the 4 week follow-up period arose because eight (73%) of the children in smoking homes had two or more symptomatic days as against 2 (18%) of the children in non-smoking homes. The data on change in use of beta-agonist therapy between weeks 1 and 4 differed from that given earlier, now being from 20.8 to 8.9 doses per week in the group with non-smoking parents and from 15.3 to 18.0 where the parents smoked ($p<0.001$).

The Davis Study

LeSon & Gershwin (1995) studied all asthmatics aged 5-12 years admitted to a medical centre over a 10 year period, excluding patients with cystic fibrosis. Of the 300 children, 55% male, 13 required intubation for their asthma. A wide range of factors possibly related to the odds of intubation were studied. Exposure to secondhand smoking (from parents, family members or room-mates) was reported by 85% of the children who required intubation and by 20% of those who did not, a highly significant ($p<0.001$) OR of 22.4 (95% CI 7.4-68.0). [From the data presented we estimate a similar OR of 22.2 but a wider confidence interval of 4.8-102.9. However the relationship is still highly significant.] It should be noted that their analysis identified 11 other factors with a significant OR for intubation, 8 with an OR above 6 and highly significant ($p<0.001$), though none with an OR as high as for secondhand smoke. Despite this, all the analyses were conducted on a one-factor at a time basis, with no attempt to determine which of the factors were independent. As with the Portland study, Chilmonczyk et al. (1993), data were available on severity but not used in analysis.

The Chicago Study

Hu et al. (1997) studied 705 fifth-graders, mainly blacks aged 10 to 11 years. 5% had ever smoked. 167 (51% male) reported having been diagnosed with asthma. Data were presented relating self-reported prevalence of symptoms and medical treatments to maternal smoking habits in pregnancy and in the past week. Among those with physician-diagnosed asthma, maternal smoking could be related to the proportion who took asthma or wheezing medication in the past 2 weeks and the proportion who attended the emergency room for treatment of asthma in the past 12 months (assuming that those who took medication or who attended the emergency room were a subset of those with physician-diagnosed asthma). The proportions taking medication or attending the emergency room were non significantly lower if the mother smoked.

Time of maternal smoking	Type of outcome	Mother did not smoke		Mother smoked		
		Outcome		Outcome		OR
		–	+	–	+	(95% CI)
In pregnancy	Took medication in past 2 weeks	25	52	15	21	0.67 (0.30-1.52)
In pregnancy	ER in past 12 months	31	46	16	20	0.84 (0.38-1.87)
In past week	Took medication in past 2 weeks	18	44	17	28	0.67 (0.30-1.52)
In past week	ER in past 12 months	24	38	19	26	0.86 (0.40-1.89)

The New Orleans Study

An abstract summarized the results of an intervention trial (El-Dahr et al., 2000) involving 16 households containing 21 smokers (at least one per household and presumably adults) and 18 asthmatic children aged 6-16 with 56% male. In phase 1 of the study the smokers smoked normally for 3 months. In phase 2 smokers received counselling and smoking cessation aids over a 1 month period in order to encourage them to quit and to cease smoking inside the home for 3 months. Although only 2 of the 21 smokers stopped completely, all of them significantly decreased the number of cigarettes smoked in phase II. The number of cigarettes smoked in the home reduced dramatically (from 18.7 to 0.18 cigs/day, $p=0.0001$), as did nicotine levels in the child's bedroom (12.8 to 1.8 $\mu g/m^3$, $p<0.0001$) and in the living rooms (53.1 to 7.3 $\mu g/m^3$, $p<0.0001$), and the cotinine levels of the parents (340.6 to 257.7 ng/ml, $p=0.002$). The cotinine levels of the children (excluding one who was found to be a smoker) did not vary materially (1.7 to 1.5 ng/ml). As regards asthma in the child, there was a significant increase in days with normal sleep (from 85% to 91%, $p<0.01$), days with normal activity (from 90% to 95%, $p<0.05$), days without cough (from 70% to 87%, $p<0.01$) and days without wheeze (from 78% to 85%, $p=0.06$). Total symptom scores decreased from 1.00 to 0.54 ($p<0.05$). Bronchodilator use was stated to have *"decreased in 7/12 (39%),"* data which are mutually inconsistent (7/12=58%) and with no significance test. There is also no statement of significance regarding average daily PEFR, though with increases in 8/15, no change in 6/15 (actually given as 6/35 but presumably a typographical error) and therefore a decrease in 1/15, we estimate p to be <0.05. FEV_1 was

noted to have improved significantly ($p<0.0001$) with 15/17 improving, but metacholine results did not vary, with as many improvements as worsenings. The limitation of this study, from a theoretical point of view, is that there was no formal control group. Had households been randomly assigned to receive or not receive cessation advice, one could have excluded the possibility that changes in asthma status may have, for example, been due to changes in the weather.

The First California Study

Based on the first stage (a cross-sectional survey) of a longitudinal study (the Children's Health Study) conducted in southern California, Li et al. (2000) related lung function in 5263 children simultaneously to sex, asthmatic status, maternal smoking in pregnancy ("*in utero* exposure") and household ETS exposure after birth, after adjustment for community, school grade, spirometer, pressure, technician, log (height), age and race. Approximately 68% of the children were fourth-graders aged 7-13 years, 16% were seventh-graders aged 11-15 and 16% were tenth-graders aged 14-19 years. The study included 442 asthmatic boys and 307 asthmatic girls. Only 13 of the 749 asthmatics were smokers themselves.

The main findings of this study were presented in three tables, one studying effects of *in utero* exposure ignoring ETS, one effects of ETS ignoring *in utero* exposure, and the third joint effects. Each table related to four measures of lung function (FVC, FEV_1, FEV_1/FVC and MMEFR) with results given separately for boys and girls and for asthmatic and non-asthmatic children. The results for single effects in asthmatic children are summarized in the table below:

		Percent change in lung function with statistical significance			
Exposure	Sex	FVC	FEV_1	FEV_1/FVC	MMEFR
In utero vs no *in utero*	Boys	-4.3**	-7.1***	-2.9*	-11.3**
	Girls	+3.3*	-0.5	-3.6***	-8.7*
Past ETS vs no ETS	Boys	-2.2	-4.9*	-2.8*	-9.2*
	Girls	+2.5	+2.1	-0.2	+1.4
One current smoker vs no ETS	Boys	-3.3	-3.9	-0.6	-4.0
	Girls	+1.9	+1.1	-0.8	+7.0
Two or more current smokers	Boys	+0.8	-2.9	-3.6	-5.2
vs no ETS	Girls	+5.9*	+2.7	-2.7	-4.2

* $p<0.05$.
** $p<0.01$.
*** $p<0.001$.

It is clear from these results that the evidence of an association was much stronger for *in utero* exposure than for ETS exposure. For *in utero* exposure 7 of the 8 estimates were of an associated reduction in lung function, with 6 of them statistically significant. The significant result for FVC in girls in the reverse direction was the only conflicting finding. For ETS exposure, the results were far less consistent, with no real evidence of any reduction in lung function in girls and significant reductions in boys only seen in relation to past, but not current, ETS exposure.

The joint effect analyses compare lung function in 5 groups:

Group	ETS	*In utero*
1 (reference)	No	No
2	Past	No
3	Current	No
4	No	Yes
5	Any	Yes

Based on these data it is possible to estimate differences associated with ETS where *in utero* exposure is not present (group 1 compared with weighted average of estimates for groups 2 and 3) and where it is present (difference of estimates for groups 4 and 5). These results (again for asthmatic children) are summarized below:

		Percent change in lung function			
Exposure	Sex	FVC	FEV_1	FEV_1/FVC	MMEFR
ETS vs no ETS	Boys	-0.2	-1.4	-1.2	-2.9
(no *in utero* exposure)	Girls	+1.7	+3.0	+1.7	+10.2
ETS vs no ETS	Boys	-2.7	-0.4	+2.2	+3.0
(*in utero* exposure)	Girls	-5.5	-1.1	+4.2	+13.6

While the significance of these individual changes cannot readily be assessed exactly from the data presented, it seems that none of the reductions associated with ETS (adjusted for *in utero* exposure) are statistically significant. Since there are as many increases as reductions in these estimates it seems that the data from this study do not show any evidence of an effect of ETS exposure independent of *in utero* exposure and little consistent evidence of an effect of ETS exposure ignoring *in utero* exposure.

The authors appear to be rather ambivalent about the conclusions of their study. In the abstract they stated *"In summary both in utero exposure to maternal smoking and ETS exposure were associated with persistent deficits in lung function. The effects of in utero exposure were greatest among children with asthma."* However, reading the last paragraph of the discussion, and most of the paper, one gets the impression that *in utero* effects were much more clearly seen and that it was not so clear whether ETS had any effect.

The Second California Study

An intervention trial (Wilson et al., 2001b) involved 87 ETS-exposed children aged 3 to 12 years (51% male) who had been seen for acute asthma in the preceding year. Following collection of baseline information, the children were randomly assigned to receive intervention (n = 44) or usual care (n = 43). The intervention involved three counselling sessions led by a nurse. These included instruction about asthma and its treatment and the role of ETS in exacerbating and sustaining inflammation, and the collection of urine for cotinine estimation, the estimates then being used at the next session as part of a review of progress in eliminating the child's exposure to tobacco smoke. The usual care also involved giving basic information about asthma and its treatment, but with no specific focus on ETS except for a generic statement that it is best avoided for children with asthma. In both groups the adequacy of medication was assessed and the regimen adjusted where necessary. Data collected from

both groups at baseline and at 6- and 12-month follow-up visits included demographic characteristics, asthma history and symptoms, medication, ETS exposure, smoking restrictions, cotinine and health care use. Lung function was collected at baseline and 12 months only.

At baseline the groups did not differ significantly ($p<0.05$) in respect of any characteristics measured, although the intervention group was almost significantly more likely to have a maternal caregiver who smoked (61% vs 42%, $p=0.07$). The main results of the study showed for each of various primary and secondary outcomes the results of "unadjusted" and "adjusted" tests of the intervention effect. The "unadjusted" comparisons involved a simple comparison of the values observed at the end of follow-up, while the "adjusted" comparisons took into account differences observed at baseline, so were equivalent to comparing changes in the two groups. The adjusted results, which seem more meaningful, showed a significant ($p=0.03$) reduction in the probability of having more than one acute medical visit in the study year in the intervention compared to control group, the percentage falling from 50.0% in the year before baseline to 29.6% in the study year in the intervention group, but rising from 37.2% to 46.5% in the usual care group. This difference was more significant ($p=0.01$) in those with 12 month cotinine data, i.e. subjects who had stayed in the study.

Although this result sounds impressive, it should be noted that there were no other significant differences. The estimated adjusted intervention effect was in the hoped for direction as regards cotinine level, hospitalisation for asthma in the year, allowance of smoking in the home, activity limitations and nights awakened, but not as regards cigarettes smoked per day at home, symptom-free days or FEV_1 (for example, FEV_1 increased by 3.72% in the intervention group but by more, 5.38%, in the control group).

Although health-care utilization had reduced more in the intervention group than in the control group, this could not be explained by a reduction in ETS exposure (as measured either by cotinine or by reported changes in smoking rules in the home). The authors noted that adjusting for either of the two indicators of ETS exposure did not affect the significant difference in reduction in health care utilization between the two groups. It would have been helpful here to present data showing, for both groups, how change in ETS exposure correlated with change in health-care utilization, but such results were not shown.

While the results seem consistent with the intervention as a whole being effective in reducing the probability of medical visits and perhaps hospitalisations, it is far from demonstrated that the reduction has actually resulted from ETS reduction. It could be, as the authors admitted, that some other part of the intervention nothing to do with ETS had an effect. The study was quite small and it would need a larger study and perhaps one in which attempts were made to *"measure ETS exposure and behavioral and disease outcomes concurrently"* before a clearer picture can be obtained.

NHANES III

In one analysis based on the Third National Health and Nutrition Examination Survey (NHANES III), Mannino et al. (2002) related indicators of asthma severity to serum cotinine level, divided into three groups (0.050 to 0.115 ng/ml = low, 0.116 to 0.639 ng/ml = intermediate, and 0.640 to 20 ng/ml = high, with 0.050 ng/ml the limit of detection and levels >20 ng/ml assumed to indicate tobacco use). 523 children aged 4-16 with physician-diagnosed asthma were involved, 59% male. After adjusting for age, race/ethnicity, SES,

family size and parental history of asthma, comparisons were made of children in the high and low cotinine group as regards various indices of asthma severity. As shown below, there was a significant positive association with moderate or severe asthma, a significant *negative* association with any hospitalisation for asthma in the previous year and a non-significant positive association with the other five indices (not all directly associated with asthma). Adjustment had little effect on the estimated ORs, though it did slightly increase and make significant the positive association with moderate or severe asthma, where the unadjusted estimate was 2.5 (0.97-6.2).

Outcome	Proportion (%)[1]	OR (95% CI)[2]
Moderate or severe asthma (symptoms/illness ≥12 days[3])	21.5	2.7 (1.1-6.8)
Severe asthma (symptoms/illness >300 days[3])	14.6	1.9 (0.6-5.7)
Any physician visit for asthma[3]	41.2	1.8 (0.9-3.8)
Any hospitalisation for asthma[3]	5.7	0.2 (0.1-0.5)
FEV_1 < 80% predicted	10.3	5.1 (0.7-40.6)
Less than very good health status	43.6	1.3 (0.7-2.5)
≥6 school absences[3]	44.4	1.8 (0.9-3.6)

[1] Proportion of all children with outcome.

[2] Comparing children with high (0.64-20ng/mL) and low (<0.116ng/mL) cotinine level.

[3] in previous year.

Comparisons were also made of the same two groups in respect of lung function, with adjustment for age, sitting height, sex, race/ethnicity, SES, parental history of allergy or asthma and family size. Three of the four parameters (FEV_1, FVC and MMEF but not FEV_1/FVC ratio) tested showed a significantly lower adjusted level in the children with high cotinine levels.

Comparing children with highest and lowest cotinine levels		
Outcome	Mean effect %	95% CI
FEV_1	-8.1	-14.7 to -3.5
FVC	-5.6	-10.6 to -0.6
FEV_1/FVC	-3.0	-6.5 to +0.5
MMEF	-12.5	-23.0 to -2.0

Results were not presented in detail for children with intermediate cotinine levels. For asthma outcomes the authors noted that ORs (compared to low cotinine) were *"similar"* to those for high cotinine, but were not statistically significant. However children with intermediate cotinine were noted to have *"lung function levels that were similar to the children with low smoke exposure."* Overall the authors concluded that *"Involuntary smoke exposure is associated with increased asthma severity and worsened lung function in a nationally representative group of US children with asthma."* They considered that the negative association of cotinine with hospitalisation in the previous year might have been *"because some parents may have altered their home smoking policies"* in response to the hospitalisation.

Another analysis based on NHANES III (Chapman et al., 2003) involved 309 children aged 8-16 with physician-diagnosed asthma, 60% of whom were male. Children who were current smokers or who had ever smoked 5 or more packs of cigarettes in their lifetime were excluded. Model-predicted lung function values were presented by the number of smokers in the home, separately for each age, for a child of defined age, race/ethnicity, height, body mass, skinfold thickness, use of gas stove, household annual income, pet ownership and physical activity. Expressing these as differences from households with no smokers in the home gives

	Girls		Boys	
	Smokers in home		Smokers in home	
	1	2+	1	2+
FVC (ℓ)	+0.107	-0.075	+0.055	-0.226*
FEV_1 (ℓ)	+0.104	-0.200*	+0.042	-0.219*
$FEF_{25-75\%}$ (ℓ/sec)	+0.065	-0.738**	+0.154	-0.163
FEV_1/FVC (%)	+0.1	-4.2*	-0.1	-1.1
$FEF_{25-75\%}$/FVC (per sec)	-0.022	-0.211**	-0.020	+0.005

* $p<0.1$.
** $p<0.05$.

These results show no association of lung function with having one smoker in the home, but some decrease with having two or more smokers in the home, with significantly ($p<0.05$) reduced $FEF_{25-75\%}$ and $FEF_{25-75\%}$/FVC in girls.

The Baltimore and Washington DC Study

The study by Morkjaroenpong et al. (2002) involved 520 children, predominantly African American, of average age 8.2 years, 40% males. The children were all reported to have doctor-diagnosed asthma, recent symptoms or a recent visit to a hospital or emergency department. Analyses compared 153 children with a caregiver who smoked in the home and 367 with no smokers in the household. Children whose primary care giver smoked but not in the home were excluded from the analysis but it is unclear how children where only other household member(s) smoked were treated. At-home ETS exposure was linked to various aspects of asthma morbidity. No significant relationship was found between smoking in the home and nocturnal symptoms, limited physical activity in the past six months, days of work missed by the caregiver in the past 6 months because of the child's asthma or school days missed by the child because of the asthma.

Further analyses were restricted to the 153 children with at-home exposure, dividing them into 71 with "moderate to high" exposure where 10 cigs/day or more were smoked and 82 with low exposure where 1-9 cigs/day were smoked. Again there was no significant association with limited physical activity, days of work missed or school days missed, but there was a significant association with nocturnal symptoms. Compared to the 43 ETS exposed children with mild intermittent symptoms (≤2 nights per month), the 32 with mild persistent symptoms (2-4 nights) [sic] had an OR of 3.4 (95% CI 1.3-8.8) for moderate to high vs low exposure, while the 78 with moderate-severe symptoms (5+ nights) had an OR of 2.3 (1.0-5.1).

These analyses were unadjusted for any potential confounding factor, but in an additional analysis the authors presented results of further analysis of nocturnal symptoms in a model that simultaneously investigated the role of the child's age, caregiver education, asthma primary care and use of anti-inflammatory medications as well as that of moderate to high vs low ETS exposure. Here the authors reported an unadjusted OR for ETS of 2.84 (1.25-6.42) and an adjusted OR of 2.83 (1.22-6.55).

The analysis was stated to relate to *"presence of nocturnal symptoms,"* but *"presence"* was undefined. The previous results seemed to imply that all the children had at least mild intermittent symptoms so it is unclear what the actual definition of the endpoint used was – perhaps it was at least mild persistent symptoms.

The analysis was also unusual in that with three ETS exposure groups – none, low, and high to moderate – it would seem more sensible to compare the second and third groups with the first group, rather than to compare the third with the second. Based on the data in the paper one can calculate the following:

	ETS exposure		
	None	Low	High to moderate
Nocturnal symptoms (at least mild persistent)			
No	83	30	13
Yes	283	52	58
OR (95% CI)	1.00	0.51 (0.30-0.85)	1.31 (0.68-2.50)
Limited physical activity past 6 months			
No	120	38	23
Yes	243	44	48
OR (95% CI)	1.00	0.57 (0.35-0.93)	1.03 (0.60-1.77)
Days of work missed in past 6 months because of child's asthma			
Mean	3.5	3.9	2.3
SD	5.4	15.3	3.0
p		NS	NS
School days missed by child because of asthma			
Mean	6.7	6.2	8.4
SD	9.0	9.9	10.9
p		NS	NS

It is interesting that when viewed in this more standard way, the data show no real indication at all of a *positive* association of ETS exposure with nocturnal symptoms or any of the asthma indices considered, the only significant differences seen being the *reduced* nocturnal symptoms and limited physical activity in the low ETS exposure group.

The Denver Study

Wamboldt et al. (2002) obtained data on ETS exposure, asthma and other variables from 152 children with asthma aged 7-18, 57% male, and from their primary parent. Children with a history of more serious medical treatments for asthma (such as 2 or more hospitalisations in last year) were excluded. A number of the asthma variables (such as asthma knowledge and age at onset) were not of interest to this review, but some were. For the 58 children with a smoker in the household (including if the asthmatic child was a smoker), compared to the 94

with no smoker in the household, no significant difference was noted in functional severity or in AQOL as reported by the child. The score for AQOL as reported by the parent was however significantly lower (poorer) (5.38 vs 6.13, $p<0.005$) where there was a smoker in the household. No adjustment was made for any potential confounding variable.

The Third New York Study

A randomized clinical trial conducted in Rochester (Halterman et al., 2004) involved 184 children aged 3 to 7 years (63% male) with mild persistent to severe persistent asthma. They were allocated to either school-based care (daily inhaled corticosteroids [ICS] provided through the school) or a usual-care group (ICS not given through the school). For 180 of the children, data were available on at home ETS exposure and on various outcomes assessed monthly for a year. Based on the combined data from the two groups, the following comparisons can be made by ETS exposure.

Variable	ETS exposure		Significance of differences[1]
	No	Yes	
Number of children	101	79	
No of symptom-free days[2]	10.97	9.69	p<0.01
No of symptom days[2]	2.07	3.07	p<0.01
No of symptom nights[2]	2.07	3.05	p<0.01
No of days using rescue inhaler[2]	1.97	2.51	NS
Overall change in AQOL[3]	0.36	0.55	NS
Total absences from school	5.92	10.28	p<0.01
			OR (95% CI)
3+ acute visits	23 (23%)	21 (27%)	1.23 (0.62-2.43)
1+ hospitalisations	6 (6%)	3 (4%)	0.63 (0.15-2.58)

[1] For the first six variables the significance is based on a t-test based on the means and standard deviations provided, although the distribution may not be normal. For the other two the significance is based on a chi-squared test.

[2] In two weeks before each monthly interview.

[3] AQOL = asthma-related quality of life. Lower scores indicate poorer quality.

The results show that, where there is ETS exposure, the children have significantly greater absences from school and days and nights with symptoms and significantly less symptom-free days. The authors also noted that effects of school-based provision of ICS (improvement in symptoms, AQOL and absenteeism) were only seen among children not exposed to ETS.

5.1.3. Description of the Studies – Canada

The Vancouver Study

In the first paper based on this study, Murray & Morrison (1986) assessed the effect of parental smoking in 94 children with a history of asthmatic wheezing. The children were aged from 7 to 17, with 65% male. Only two admitted to smoking. There were 24 whose mother smoked and 70 where the mother was a non-smoker, the two groups being similar on age, gender and various confounding variables. Children whose mothers smoked had, on average, a 47% higher asthma history severity score (p=0.001), a 13% lower FEV_1 (p=0.004), a 23% lower $FEF_{25-75\%}$ (p=0.005) and, in a subgroup of 41 children whose values were not influenced by recent bronchodilator medications or by respiratory infections, an almost five-fold greater responsiveness to histamine (p=0.002). FVC was not significantly related to maternal smoking in all 94 children, but in the subgroup of 41 it was 12.6% lower (p=0.002) if the mother smoked. In all 94 children and in the subgroup, there was a significant dose-response to the number of cigarettes smoked by the mother at home for FVC, FEV_1, $FEF_{25-75\%}$, symptoms and responsiveness to histamine. The differences between the children of smoking and non-smoking mothers were greater in older than in younger subjects. In contrast there was no significant relationship of father's smoking to any of these indices of asthma severity, there being 28 children whose father smoked.

In an increased sample from this study, Murray & Morrison (1988) studied the effect of parental smoking in 240 non-smoking children with a history of asthmatic wheezing. The children were of age 7 to 17, with 68% male. As in the previous paper (Murray & Morrison, 1986), the overall data showed a strong relationship of maternal smoking to pulmonary function and bronchial responsiveness (symptom data not being reported this time), but little relationship to paternal smoking. There were 56 children with a mother who smoked and 183 with a non-smoking mother. Apart from the size of mite test reaction being smaller if the mother smoked ($p<0.01$), there was little difference between the two groups in potential confounding variables. Children with a smoking mother had a lower FEV_1 (76% vs 85%, $p<0.01$), a lower $FEF_{25-75\%}$ (59% vs 73%, $p<0.01$) and a lower PC_{20} (0.91 vs 2.03, p=0.01). There was also a strong correlation with the number of cigarettes smoked by the mother. Smaller differences were seen in relation to father's smoking and they were not statistically significant.

An interesting feature of the study is the separate analyses conducted according to whether or not the readings were taken in the cold, wet season (October-May), when windows would tend to be closed and ETS exposure higher, or in the warm, dry season (July-September), when windows tend to be open and exposure lower. The analyses showed a clear association of maternal smoking with pulmonary function (FEV_1 and $FEF_{25-75\%}$), bronchial responsiveness (PC_{20}) and recent use of bronchodilator medication in the cold, wet season, but no such association in the warm, dry season. These results were confirmed by analyses adjusting for potential confounding variables.

A third paper from this study (Murray & Morrison, 1989) was based on 414 non-smoking asthmatic children aged 1 to 17 (70% male) who had a mother with known smoking status. Only children aged 6+ underwent lung function testing, 294 producing an acceptable spirogram. As in the previous paper (Murray & Morrison, 1988) children of non-smoking mothers (n=322) and of smoking mothers (n=92) were comparable apart from the latter group of children having a smaller mite test wheal. Children of smoking mothers had a significantly

higher asthma symptom score (8.8 vs 6.4, p<0.01), lower FEV_1 (77.3% vs 84.4%, p<0.01) lower $FEF_{25-75\%}$ (59.5% vs 71.7%, p<0.01) and lower log PC_{20} (-0.14 vs 0.71, p=0.01) and a non-significantly lower FVC (91.2% vs 93.8%, p=0.2). Although the differences were in the same direction in relation to smoking by the father, they were not statistically significant at p<0.05.

The main purpose of this paper was to investigate how the association with maternal smoking varied by the sex and age of the child. Associations tended to be stronger in boys than in girls and stronger in older than younger children. Although on some occasions differences according to maternal smoking status were significant for boys and not girls or for older and not younger children, the authors never actually carried out statistical tests of interaction. Based on the data presented we find that none of the differences between smoking and non-smoking parents vary significantly by the sex of the child and only for PC_{20} does the difference clearly vary significantly by age. As a result of this, we believe that the authors may have rather over-interpreted their data when they concluded that *"compared with girls, boys were more sensitive to passive smoking, and that its adverse effect increased with age and with duration of exposure."*

A fourth paper from the study in Vancouver (Murray & Morrison, 1992) concerned 240 non-smoking asthmatic children aged 7 to 17. As reported previously (Murray & Morrison, 1986; Murray & Morrison, 1988; Murray & Morrison, 1989), children whose mothers smoked had significantly more severe asthma. Since the children analysed in this paper are a subset of those described in the third paper (Murray & Morrison, 1989), the results add little new. The purpose of the paper was to investigate the effect of maternal smoking on asthma severity separately for those children who did or did not have atopic dermatitis, the analyses concluding that atopic dermatitis had no effect on asthma severity and that there was no interaction of atopic dermatitis with maternal smoking on severity.

The final paper from the study (Murray & Morrison, 1993) concerned 807 non-smoking children with asthma aged 1-17 years referred between 1983 and 1990. Comparisons were made of the 415 children seen before July 1986, and the 392 children seen afterwards. Doctors referring patients to the clinic have, since 1985, been urged to counsel parents of asthmatic children never to smoke when in the home. The main findings of the study were as follows:

- Although the total number of cigarettes smoked per day by parents was similar for the two periods, there was a highly significant drop in the number of cigarettes reported to be smoked in the presence of the child, from 7 to 3 for the mother, and from 5 to 2 for the father.
- Where the mother was a smoker, there was a highly significant (p<0.001) decline in the asthma score and increase in FEV_1 and $FEF_{25-75\%}$ between the two periods. In contrast, where the mother was a non-smoker, there was no decline in asthma score, and a smaller increase in lung function. A similar pattern was seen in relation to paternal smoking except that the decline in asthma score was not significant.
- The number of cigarettes reported to be smoked in the presence of the child by the mother was significantly correlated with the child's asthma score (positive) and with the two indices of lung function (negative). Similar correlations with paternal smoking were also significant for lung function but not for asthma score.

- Adjustment for sex, age, and age of onset of asthma confirmed the relationships noted in bullet point 2 above. Further adjustment for number of cigarettes smoked by the parents when in the same room as the child reduced the significance of the association.

The authors concluded that *"there is evidence that since 1986 an increasing awareness of the harmful effects of second-hand smoke has caused parents to smoke fewer cigarettes when with their asthmatic children, and that the resulting decrease in exposure has been associated with a marked improvement in the severity of asthma of the smokers' children who have been referred to our clinic."*

In considering these results, some important points should be made. Firstly, smoking habits of the parents were usually provided only by the mother and were unvalidated. It seems possible that at least part of the reported reduction in smoking in the presence of the child by the parents may have resulted from increasing denial. After all, there is abundant evidence in the literature that people advised by their doctor to give up smoking frequently falsely admit that they have done so (Lee, 1988). A similar scenario seems likely to exist if, as here, the doctor advised parents not to smoke in the presence of the child.

Second, the study showed no real evidence at all that bronchial hyper-responsiveness, as measured by the PC_{20} test, was associated with smoking by the parents or that it decreased between the two periods.

Third, on inspecting the detailed results presented, a striking fact emerges, namely that though in the first period the mean asthma score was highly significantly ($p<0.001$) *higher* if the mother smoked (mean 8.2, SE 0.3) than if the mother did not smoke (mean 6.4, SE 0.2), in the second period the mean asthma score was actually significantly ($p<0.05$) *lower* if the mother smoked (mean 5.8, SE 0.2) than if the mother did not smoke (mean 6.6, SE 0.2). The authors failed to mention this point, which seems inconsistent with their thesis. It is also true that, while before July 1986 pulmonary function was much lower if the mother smoked, after July 1986 it was very similar in children whose mothers smoked or did not smoke.

Finally, and importantly, one can compute from the results presented the following differences between the two time periods for children where the parent smokes:

	Difference post- vs pre-July 1986	
	Unadjusted[1]	Adjusted[1]
Asthma score	-0.99	-1.02
FEV_1%	+14.5	+11.4
$FEF_{25-75\%}$	+14.7	+11.95

[1] For number of cigarettes smoked in same room as child.

It can be seen that only a small proportion of the difference in recorded response between the two time periods (and essentially none of it as regards asthma score) can be explained by the parents smoking less in front of their children. This is in direct contrast to the authors' claims. Although there has been a marked improvement in asthma score and lung function over the period in children of smokers, it appears to be mainly due to reasons other than reduced smoking by the parents in the child's presence. It is also notable from the data presented in the paper that there were quite substantial improvements in lung function (though not in asthma score) over the time period in children whose parents do not smoke.

Generally, the paper must be regarded as unconvincing, with parts of the data inconsistent with the authors' claims not really brought to the reader's attention.

The Toronto Study

MacArthur et al. (1996) studied 68 children of median age 3 years, 71% male, who had their first ever admission for treatment of asthma in a defined 19 month period and who had been readmitted to the same hospital because of asthma within 12 months of the first admission. This cohort was followed forward, and their probability of readmission within 12 months of the second discharge related to a variety of risk factors. 17 of the 30 (57%) subjects with one or more smokers in the home qualified in this respect, as against 15 of the 38 (39%) with no smokers in the home. This represented a non-significant relative risk of 1.44 (95% CI 0.87-2.37).

The Edmonton Study

Mayo (2001) compared 31 children of mean age 6.4 years, 17 male, who had been admitted to a pediatric unit with an acute exacerbation of asthma of non-infectious origin and who had one or more parents who smoked at least a pack a day with 31 age- and sex-matched controls also with an acute exacerbation of asthma, but without such ETS exposure. Though the study principally concerned theophylline clearance, it was noted that the duration of the hospital stay was significantly ($p<0.05$) longer in the ETS-exposed group (4.35 vs 2.86 days). The author concluded that *"Clinically, passive smoke exposure resulted in a longer hospital stay"* without discussion or consideration of potential bias and confounding.

The Nine Region Study

A study in nine health units/departments across Canada (Dales et al., 2002) involved 3010 schoolchildren aged 5-19 years with current asthma, 52% of whom were male. The OR for having a hospital visit for asthma in the last 12 months in relation to regular ETS exposure at home was 1.55 (95% CI 1.22-1.97) in unadjusted analyses. The OR was noted to vary by household income (<$20000 1.79, $20000 to $60000 1.35, >$60000 1.45) although this variation did not appear to be statistically significant.

5.1.4. Description of the Studies – Europe

England: The Sheffield Study

In a case-control study, Strachan & Carey (1995) compared 486 secondary-school children who, in an earlier study two years before, had reported that over the previous 12 months they had suffered either 12 or more wheezing attacks or a speech-limiting attack of wheeze (over 90% of whom had doctor-diagnosed asthma) to 475 children with no history of asthma or wheeze, frequency matched for age and school class. While comparison of cases and controls is not relevant to exacerbation of asthma, tables are presented which allow comparison of parental smoking habits among 113 children with frequent and speech-limiting wheeze ("severe cases") and children with frequent or speech-limiting wheeze but not both ("less severe cases"). As shown in the table below, there was a significant tendency for severity of asthma to be greater if either the mother or the father smoked. However no dose-

relationship was evident. The authors reported that results were similar for maternal smoking around the time of the child's birth, but did not present any details.

		Smoking habits (cigs/day)			
Parent	Asthma	0	1-10	>10	Any
Mother	Less severe	289	57	27	84
	Severe	75	25	13	38
	OR	1.00	1.69	1.86	1.74
	(95% CI)		(0.99-2.88)	(0.91-3.77)	(1.10-2.76)
Father	Less severe	313	39	20	59
	Severe	85	18	9	27
	OR	1.00	1.70	1.66	1.69
	(95% CI)		(0.93-3.12)	(0.73-3.77)	(1.01-2.82)

England: The North East England Study

Shamssain & Shamsian (1999) collected data on 3000 children aged 6-7 years from parents or guardians on smoking habits and on prevalence of various respiratory symptoms. About 685 children (59% male) had ever had asthma. The prevalence of ever asthma in the children was 20.6% if no parent smoked, 26.4% if one parent smoked and 28.7% if both parents smoked. Corresponding prevalences of limitation of speech during attacks in the past year were 2.7%, 3.7% and 4.3%. This implies that, among the asthmatics, the corresponding proportions with speech limitation were 13.1%, 14.0% and 15.0%, differences which are clearly not significant.

Finland: The Kuopio Study

Schwartz et al. (2000) studied 74 asthmatic children aged 7-12, 61% male. For three months the children measured their PEFR every morning and evening and kept a daily diary of respiratory symptoms. They also noted daily whether they had used respiratory medication and whether someone had smoked inside their home. When the data were analysed longitudinally, ETS exposure at home was associated with significant reductions in morning PEFR of 41.9 ℓ/min (95% CI 9.5 to 74.3 ℓ/min) and in evening PEFR of 40.7 ℓ/min (7.6 to 73.7 ℓ/min) after adjustment for age, height, sex, atopic status, father's education, weight, use of maintenance drugs, day of study, previous day's temperature and humidity, bronchodilator use, a random-subject effect, and whether the measurement was taken on a weekend. Similar estimates were obtained using a cross-sectional model. Adjustment for atopic status, use of maintenance drugs or bronchodilator use made little difference to the estimates, but failure to adjust for father's educational level would have led to markedly lower estimates of 26.0 ℓ/min for morning PEFR and of 23.8 ℓ/min for evening PEFR. Evidence was also presented to support the existence of a dose-related relationship (trend p=0.01) between PEFR and the percentage of days with ETS exposure. The above analyses were based on between-child comparisons. Within-child comparisons showed that ETS exposure on a given day was on average associated non-significantly with a lower PEFR the next day by about 10 ℓ/min.

The previous day's ETS exposure was a significant risk factor for need for bronchodilator use on any given day (OR 10.3, 95% CI 1.3-83.7). Mean ETS exposure over the previous two days was associated with a significant increase in the probability of cough (12.4, 2.4-63.3)

and of phlegm production (7.8, 1.4-41.7). Wheezing/breathing difficulties were too rare for analysis.

The authors concluded *that "exposure to ETS was associated with a decline in peak flow and increase in symptom reporting and use of bronchodilator drugs by asthmatic children. The effect of ETS on PEFR in this study was largely chronic, but evidence for an effect of daily variations in ETS was seen for bronchodilator use and respiratory symptoms, and there was a suggestion of an acute effect on PEFR."*

France: The Marseilles Study

Dubus et al. (1998) studied 46 asthmatic children with a positive skin prick test (SPT) to one or more common aeroallergens, normal spirometric values and no upper airway infection. The children were aged 5 to 14 (mean 8.3), with 57% male. Parents were instructed to withhold any asthma therapy for 24h before the tests. Comparisons were made between 23 children with detectable and 23 with non-detectable cotinine in urine, based on a limit of detection of 1 ng/ml. No child was considered an active smoker based on the cotinine values (maximum = 98 ng/ml). There was no significant difference between the exposed (detectable cotinine) and unexposed groups in respect of the number of crises per year (4.1 vs 4.4), symptoms between crises (OR 0.49, CI 0.15-1.60) or use of anti-inflammatory treatment (0.66, 0.19-2.35). There was also no significant difference as regards FEV_1 (106.5% vs 101.9%, p=0.2), FVC (106.6% vs 101.7%, p=0.13), PEFR (89.1% vs 85.6%, p=0.56), $FEF_{25-75\%}$ (94.0% vs 104.3%, p=0.34), or SRAW (7.6 vs 7.4 cm H_2O/s, p=0.30). The doubling dose (PC_{100} SRAW) was determined, and was significantly less in the exposed group (108.3 vs 160.9 µg, p=0.04). Following administration of 200 µg albuterol, the percentage of bronchodilatation was defined from the difference between the largest SRAW value obtained and the SRAW value measured 15 minutes later divided by the largest SRAW value. This was significantly higher in the exposed group (74.8% vs 68.8%, p=0.03). No significant relationship was reported between parental smoking and either the doubling dose (mother smoked 98.4 vs 147.2 µg) or the percentage of bronchodilation (data not given). The authors concluded that *"environmental tobacco smoke increases bronchial reactivity in asthmatic and allergic children."*

A further report from Marseilles (Oddoze et al., 1999) concerned 90 children with suspected asthma, aged 4 to 14 (mean 8), with 60% male. The authors noted that urinary cotinine was not associated with basal spirometric tests (FEV_1 and SRAW). Bronchial responsiveness to carbachol was significantly associated with cotinine (p=0.03), but not CCR (p=0.07) or the number of cigarettes smoked by the parents (p=0.19). Detailed results were not reported. Despite these rather marginal results, the lack of consideration of any potential confounding variables and the fact that only 33% of the children had clinical asthma, the authors concluded that *"Passive smoke exposure increases the bronchial responsiveness to carbachol in asthmatic children."* Whether the samples of children studied in this and the previous paper are separate is unclear.

France: The Nationwide Study

A prospective study conducted by chest specialists throughout France (Soussan et al., 2003) involved 167 children aged 6-12 years (64% boys) with recently diagnosed mild or moderate persistent asthma who had been prescribed inhaled anti-inflammatory treatment.

Starting one year after recruitment, the children were followed-up for a further 2 years, with a visit every 4 months. PEF was measured twice a day during the week before each visit. Two endpoints were studied: (1) symptom control = having diurnal or nocturnal exacerbations less than once a week and no symptoms between exacerbations, at all visits and (2) PEF control = daily PEF variability <20% on each of the seven days before each visit. Symptom control was achieved by 42 children and PEF control by 89. 28 factors were considered, of which 10, including the ETS variable at least one smoker in the home, were related to symptom control in univariate analysis ($p<0.2$) and were included in a multiple regression analysis. Three factors remained significantly ($p<0.05$) related to symptom control – taking the prescribed doses (OR = 4.82, 95% CI = 1.87-12.4), understanding how the medication works (3.38, 1.18-9.64) and at least one smoker in the home (0.34, 0.13-0.91). Similarly, of 9 factors, including the ETS variable mother smoking in the home, identified in the univariate analysis for PEF control, taking the prescribed doses (3.58, 1.68-7.67), moulds within the home (0.33, 0.11-0.97) and mother smoking in the home (0.34, 0.14-0.89) remained significant in the multivariate analysis. Although taking the prescribed doses was a major factor for both endpoints, no information was presented on whether children with smokers in the home were more or less likely to take the prescribed doses (or understand how the medication works). It should be noted that the endpoints can be seen as inversely related to asthma severity/exacerbation.

Germany: The Freiburg Study

Frischer et al. (1992) investigated the relationship between maternal smoking and bronchial hyperresponsiveness (as assessed by a decrease of 15% or greater in PEFR following a standardized free running test) in 1461 primary school children of mean age 7.3 years. 171 of the children were asthmatics. Among this group the prevalence of bronchial hyperresponsiveness was non-significantly higher if the mother smoked in pregnancy (22.2% vs 14.5%) or if the mother smoked in the child's first year (24.2% vs 13.5%), but was non-significantly lower if the mother smoked in the child's eight year (9.5% vs 17.7%). In a multivariate analysis involving prematurity, pneumonia during the first year of life, atopy, education and sex of the child, the authors reported no significant relationship to maternal smoking in pregnancy (OR 2.20, 95% CI 0.29-16.57), a significant and huge positive relationship to maternal smoking in the child's first year (20.56, 2.5-168.9) and a significant and huge negative relationship to maternal smoking in the child's eight year (0.05, 0.005-0.61). It seems to us that these analyses may be unstable due to the strong correlations between maternal smoking at the various time points, and that the association of ETS with bronchial hyperresponsiveness is unclear from these data. However, the authors cited the findings in the abstract, noting the very strong positive OR with maternal smoking in the child's first year, but also noting that *"current exposure to maternal smoking was associated with less hyperresponsiveness."* They commented that *"The effect of current maternal smoking might reflect changes in smoking habits by mothers of children with symptoms, whereas exposure to tobacco smoke in early life might be causally related to bronchial hyperresponsiveness,"* and concluded by stating that *"Our findings support the general hypothesis that early lung injuries have an impact on the later respiratory health of children."*

Meinert et al. (1994) presented essentially the same findings two years later, though the results, with ORs of 1.3 for mother smoked before pregnancy, 1.7 for smoking during

pregnancy, 2.2 for smoking in the child's first year and 0.5 for smoking in the child's eighth year, were based on separate analyses. The authors reported a significant (p=0.02) association between bronchial hyperresponsiveness and changes in maternal smoking habits between the child's first and eight years.

Change in smoking habit	Percentage of children with BHR	Percentage of children without BHR
Began smoking after pregnancy	20	8
Began smoking between 1st and 8th year	0	12
Stopped smoking between 1st and 8th year	16	3

BHR = bronchial hyperresponsiveness.

Based on the same study, Frischer et al. (1993) reported the relationship of maternal and paternal smoking to PEFR variability based on 991 of the 7 year old children (48% male), 113 of whom were asthmatic. The PEFR was measured twice daily over a 1 week period, with the log of a week's mean of daily amplitude calculated as an index of variability. In multivariate analysis, only current maternal smoking and atopy were found to have a significant relationship to PEFR variability. For asthmatic children without atopy (n=80), PEFR variability was 54.7% higher (95% CI +5.5% to +226.8%) if the mother smoked, whereas in atopic asthmatic children (n=33), it was 8.5% lower (95% CI –41.2% to +42.3%). In the latter group there was evidence that mothers changed their smoking habits subsequent to the development of disease in their children. The authors concluded that *"exposure to maternal smoking can increase the variability of PEFR and thus might contribute to the development of asthma."*

Germany: The Lower Saxony Study

Seidler et al. (1998) studied 600 asthmatic children aged up to 8 years who had attended a doctor in a baseline phase in 1991. 218 (65% male) of the children had visited the same doctor about 3 years later during a follow-up phase. There were 200 children with information on progression of the asthma; 29% with no attacks, 45% with a decreasing frequency of attacks over the 3 years, 20% in which the frequency had remained the same and 7% in which it had increased. In a polytomous logistic regression analysis involving a number of other variables (age, sex, parental education, frequency of asthmatic episodes, infection-associated asthma, "asthma on exertion," neurodermitis of the child, hospital stay, speciality of treating physician, adequacy of medication, parental asthma, sensitivity to exhaust gases and region) smoking in the home was associated with a marginally significant (p=0.05) increased risk of an unfavourable course of the disease, with an OR of 1.7 (95% CI 1.0-3.0). It is not totally clear to these reviewers whether all variables were considered simultaneously in the analysis or whether Table 3 of the source paper presents the results of univariate analysis. As a multivariate analysis it would have some objections in that asthma endpoints seem to be included both as independent and dependent variables. An association was reported between having more than five asthmatic episodes in the last 12 months and a worsening course of the disease, but these variables to some extent measure the same thing. The authors did not include any simple table relating smoking in the home to progression of the asthma. The paper also reported an almost significant ($0.05<p<0.1$) difference in the

prevalence of smoking in the home for the 382 children not followed up (42%) and the 218 followed up (34%). This highlights the possibility of some selection bias.

Italy: The Viterbo Province Study

Martinez et al. (1988) studied the relationship between parental smoking, asthmatic status, atopy and bronchial responsiveness in 170 unselected schoolchildren aged 9, 49% of whom were boys. The relationship of bronchial responsiveness (as determined by a carbachol inhalation test to obtain a drop in FEV_1 of 20% or more) to parental smoking in the whole population was significant (p=0.036) after controlling for sex and atopy. In the 22 asthmatic children, the same relationship was significantly (p=0.02) stronger, with the OR for bronchial responsiveness for parental smoking estimated as 18.7 (1.5-232.3), based on 14/17 responders where a parent smoked and 1/5 responders where no parent smoked.

Netherlands: The Zwolle Study

Meijer et al. (1996) studied 55 children of mean age 9.3 years, 60% boys, who had symptoms of asthma, increased total IgE, an allergy to house dust mite (HDM) but not to dog, cat, tree, grass or milk, an $FEV_1 \geq 70\%$ of the predicted value and increased bronchial responsiveness to histamine. The children all had asthma symptoms well controlled by daily ICS and β_2-adrenergic drugs if needed. PEFR amplitude (mean % over a 24 hour period) was obtained during and 6 days after withdrawal of ICS. 26 of the 55 children had a parent who smoked. PEFR amplitude in relation to ETS (from parental smoking) and ICS withdrawal was as follows:

		Median (Minimum-Maximum) PEFR amplitude	
Exposure	n	During ICS	After ICS withdrawal
No ETS	29	20.6 (5.7-63.4)	19.4 (0.0-56.5)
ETS	26	28.7 (10.7-99.0)	29.7 (3.9-56.6)
Significance of difference[1]		Not significant (p>0.05)	p<0.05

[1] From Mann-Whitney U test.

The authors noted that *"children exposed to ETS … had significantly higher PEFR amplitudes after withdrawal of ICS than did nonexposed children"* and that *"This was not found during ICS"* and concluded that *"exogenous stimuli such as exposure to ETS … contribute to an increased circadian PEFR amplitude after withdrawal of ICS and therefore to nocturnal worsening of asthma in HDM-allergic asthmatic children."* But the difference in medians between ETS and non-ETS exposed children is in fact very similar during ICS (28.7-20.6 = 8.1) and after ICS withdrawal (29.7-19.4 = 10.3) and is clearly not significantly different.

The authors also reported the results of a multivariate analysis investigating factors associated with PEFR amplitude after withdrawal of ICS. Although the difference associated with ETS increased only slightly, from 10.3 to 11.2, the p value now became highly significant (p<0.001). The authors also noted an interaction between the effects of ETS and of bronchial responsiveness on PEFR amplitude after ICS withdrawal, finding a significant association between ETS and PEFR amplitude only in those with an above average bronchial responsiveness (p=0.008). Given that the difference in amplitude associated with ETS exposure is only significant at p=0.05 for those with above average responsiveness, and that

the difference is in the same direction for those with below average responsiveness, it is difficult to see how the interaction is in fact significant at all, let alone significant at p=0.008.

Apart from these doubts about the validity of the statistical analysis, one must also wonder how the endpoint of the study, PEFR amplitude, actually relates to exacerbation of asthma. It should be noted that their own data showed no relationship of FEV_1 to PEFR amplitude.

Portugal: The Lisbon Study

Gaspar et al. (2002) compared 124 children admitted to a hospital for acute asthma during a two-year period (mean age 4.1 years, 57% male) to 124 outpatients individually matched on age, sex and socio-economic status. In univariate analyses asthma admission was significantly associated with parental smoking (OR 3.51, 95% CI 2.1-6.0), paternal smoking (3.0, 1.8-4.9), maternal smoking (1.8, 1.0-3.1, p=0.02) and with any ETS exposure (4.59, 2.6-8.0), but not with other residents at the home (1.28, 0.8-2.0). Similar relationships were seen when analysis was restricted to the 74 pairs of children under 4 years of age – e.g. for any ETS exposure (5.0, 2.3-11.4). In a multiple logistic regression analysis involving all the children, any ETS exposure remained a significant predictor of asthma admission (6.63, 2.5-17.8) after adjustment for prior asthma hospitalisation, atopy, maternal asthma, last year asthma admission, onset of symptoms before 12 months of age, attendance at day care or kindergarten, and family size.

Scotland: The Tayside and Fife Study

Crombie et al. (2001) studied 438 asthmatic children aged 2-12, 66% of whom were male and all having one or more parents who smoked. They had previously taken part in a randomised controlled trial of advice aimed at reducing passive smoking. Information on health service contacts for asthma over the previous 12 months was collected and a saliva sample taken for cotinine determination. In a multivariate model including age, severity of asthma (perceived, and based on treatment) and number of children in the household, there was no clear relationship of cotinine to the frequency of contacts for asthma, with incidence rate ratios of 0.95 (95% CI 0.82-1.11) for medium cotinine (2.1-4.5 ng/ml) and of 1.15 (0.98-1.34) for high cotinine (>4.5 ng/ml) as compared to low cotinine (≤2.0 ng/ml). In the same model, there was a significant tendency for the incidence rate ratio to be reduced if the mother only smoked (0.76, 0.64-0.89) or if both parents smoked (0.78, 0.66-0.93) compared to if the father only smoked. In earlier univariate analysis, the authors had also reported a highly significant negative relationship with the amount smoked in the home by the index parent, with incidence ratios of 1.00, 0.81, 0.70, 0.74 and 0.66 for, respectively, 0-5, 6-10, 11-15, 16-20 and >20 cigarettes/day, although amount smoked in the home did not appear in the final multivariate model. The authors concluded that *"High levels of parental smoking in the home are associated with a reduction in health care contacts for asthma. This could be due to a lack of awareness of asthma symptoms among heavy smokers or a reluctance to visit the GP. Children with asthma who have parents who smoke heavily may not be receiving adequate management."* [GP is general practitioner.]

Spain: The San Sebastian Study

Callén et al. (1997) studied 312 asthmatic children aged 3-19 years (mean 9.01), comparing 187 cases satisfying at least one of the following criteria: FVC < 85%, FEV_1 < 85%, PEFR < 85% or $FEF_{25-75\%}$ < 60%, and 125 controls satisfying none of these. One or more parents smoked in 70.1% of the cases and 56.0% of the controls, giving an OR of 1.84 (95% CI 1.12-3.03). The authors also presented a table comparing pulmonary function variables according to at home ETS exposure, presumably based on all 312 children. For all four variables, values were lower in the exposed group (FVC 96.9% vs 97.4%, FEV_1 91.9% vs 93.7%, PEFR 87.2% vs 92.6%, $FEF_{25-75\%}$ 72.2% vs 76.7%) but none of the differences were statistically significant, with the p values >0.2 for each comparison. Despite this lack of association, one of the conclusions was that *"pulmonary function in asthmatic children is influenced by parental smoking habits."* The basis for this conclusion is not apparent. COHb was measured in both children and parents. Though results were presented which found that smoking parents had higher COHb, it seems somewhat surprising that the child's COHb was not compared in the two groups of asthmatic children.

Sweden: The Stockholm Study

In an abstract describing a two-year follow-up of a study of asthmatic children Melén et al. (2000) reported results for 144 of the original 189 children. 12 children of mean age 44.3 months were assessed as having severe asthma (based on symptoms and use of inhaled steroids) and 132 children of mean age 49.5 months were assessed as having mild/moderate asthma. Parental smoking was one of a number of variables recorded at baseline (age 1-4) associated with an increased risk of severe asthma at follow-up (age 3-6), with a relative risk estimated as 2.7 (95% CI 0.8-9.8). Parental smoking at follow-up was also stated to have no significant association. It was not stated whether these analyses were adjusted for potential confounding factors. Although the relative risks for parental smoking were not statistically significant the authors nevertheless concluded that *"In children with induction of asthma during the first two years of life, early sensitization, cat allergen exposure at home and parental smoking seem to increase the risk for development of severe asthma with regular use of inhaled steroids later in childhood."*

Later Melén et al. (2001) reported results based on 181 asthmatic children aged 1-4, 76% male, who were followed up for 2 years. Of 12 children satisfying the criteria for current severe asthma at follow-up, 9 (75%) had reported ETS exposure at home at baseline whereas, of 158 children with mild/moderate asthma, 85 (54%) did. This was reported as a non-significant OR of 2.59 (95% CI 0.73-9.14) [though from the data presented we calculate it as 2.58 (0.67-9.87)]. After adjustment for age, heredity, and exposure to cat, dog and windowpane condensation, the OR increased to 3.01 (0.74-12.2) but remained non-significant. The unadjusted OR is equivalent to a relative risk of 1.39 (0.61-3.18). The number of children with severe asthma is too small to make any firm conclusion, though the authors noted that *"In young asthmatic children, early exposure to … tobacco smoke increased the risk of … further development of more severe asthma later in childhood."* The subjects in this study possibly include those described in the earlier abstract.

5.1.5. Description of the Studies – Asia (Including Turkey)

China: The Anqing Study

Venners et al. (2001) studied 529 never smoking asthmatic children aged 8 to 15 years of age whose mother was a never smoker. 50% of the children were male. As shown in the table below, both in girls and boys, paternal smoking was associated with some reduction in FEV_1 and FVC after adjustment for age, height, height squared, weight and father's education. However these relationships were not statistically significant.

		Decrement in FEV_1 or FVC by father's smoking habits[1]		
Endpoint	Sex	Never	<30 cigs/day	30+ cigs/day
FEV_1	Boys	0 (base)	-1.9%	-3.7%
	Girls	0	-1.0%	-1.3%
FVC	Boys	0	-1.8%	-3.7%
	Girls	0	-0.4%	-0.8%
		Number of subjects		
	Boys	48	179	38
	Girls	50	185	29

[1] Ex-smoking fathers were excluded.

The authors stated that they also investigated the ratio of FEV_1 to FVC but did not find an important association.

India: The New Delhi Study

Ratageri et al. (2000) studied 60 children suffering from severe chronic asthma and 60 children suffering from mild chronic asthma. The children were aged 5-15 years with 72% male. On univariate analysis there was a tendency for the odds of severe asthma to be increased if family members smoked, particularly 10+ cigs/day. In multivariate analysis involving age of onset of asthma, past history of lung diseases, family history of asthma, allergy, breastfeeding, overcrowding, pets, cooking, worm infestation, eosinophil count and air pollution, smoking by the family did not emerge as a factor associated with severity of asthma.

	Mild		Severe		
Smoking by the family	No	Yes	No	Yes	OR (95% CI)
Any family member	32	28	26	34	1.49 (0.73-3.07)
Father	38	22	31	29	1.62 (0.78-3.35)
Grandfather	55	5	54	6	1.22 (0.35-4.24)
Cigs/day smoked by family:					
None		23		26	1.00
1-9		13		7	0.66 (0.23-1.90)
10		15		27	2.22 (0.98-5.01)

Lebanon: The Tripoli Study

A retrospective study (Kalaajieh, 2002) involved 288 asthmatic children between 6 and 15 years of age, 64% male, who were hospitalised over an 8 year period. Data on ETS exposure at birth and other factors were recorded at the time of first admission and related to the rate of further admissions by the end of the period. 68 of the children had a mean of more than one further admission per year. In univariate analyses, 13 factors were identified as having a significant association with multiple admission. These included maternal smoking (OR 6.10, 95% CI 2.98-12.55) and indoor smoking (3.06, 1.81-5.18), and also sex, age, residence, frequent respiratory tract infection, atopic dermatitis, allergic conjunctivitis, allergic rhinitis, family history of allergy, total serum IgE, eosinophils in peripheral blood and household number. Although many of these associations were very strong and highly significant (e.g. atopic dermatitis 11.93, 5.81-24.53), only two factors were found to be significant in a multiple logistic regression analysis – maternal smoking and recurrent URI (both $p<0.001$; ORs not given).

Saudi Arabia: The Al-Majmaah Study

Al-Ghamdy et al. (2000) studied 606 children with asthma aged up to 13 years, 69% male. 292 of these were infants aged less than 1 year. The authors presented a table relating asthma severity (based on national guidelines) to parental smoking from which the relative risks given below were calculated and showed a significant relationship. No attempt was made to adjust for potential confounding factors.

	Asthma severity		
Parental smoking	Mild	Moderate	Severe
No	279	30	29
Yes	190	37	41
OR	1.00	1.81	2.08
(95% CI)		(1.08-3.03)	(1.25-3.46)

Taiwan Study

In a study of 46 asthmatic children reported only as an abstract (Chan & Chen, 1995) peak expiratory flows (PEFRs) were measured at night and in the morning daily over a 6 month period, a PEFR lower than 80% of predicted being defined as an asthmatic attack. The CCR of urine samples collected at different PEFR levels was used as a biomarker for ETS exposure. The CCR associated with a PEFR ratio <0.8 was stated to be significantly higher than that associated with a PEFR ratio >0.8 (13.95 vs 7.09 ng/mg) for urine samples collected in the night, though the actual significance level was not given. There was also a significant trend in CCR increase as the PEFR ratio decreased. The abstract does not make clear how the multiple data per subject have been dealt with, and whether the analyses have been based on within- or between-subject comparisons. The data clearly have the potential to test whether, within-subject, PEFR varies by CCR, which would be valuable to know.

Turkey: The First Istanbul Study

A study reported only as an abstract (Güler et al., 2000) involved 47 asthmatic schoolchildren aged 5 to 15 years, with 68% boys. A questionnaire determined the amount and time of exposure to ETS, and the urinary CCR was determined. The patients were

followed up for one year and pulmonary function was determined regularly. The abstract states that there was no correlation of asthma severity or pulmonary function to CCR. Asthma severity was, however, significantly correlated with the number of cigarettes smoked by the mother currently (p=0.008), by the mother during pregnancy (p=0.006), and by the father (p=0.04) and with the amount of passive smoking of mothers during pregnancy (p=0.04). $FEF_{25-75\%}$ reversibility (undefined) was significantly higher if the mother smoked currently (p=0.03) and during pregnancy (p=0.001). PEF reversibility (not defined) was significantly higher if the mother smoked during pregnancy (p not given). The authors considered that they *"have established that ETS, primarily smoked by the mother during various periods of life have (sic) long term effects on clinical features of asthma in schoolchildren."* They did not comment on the inferences to be drawn from the fact that an objective indicator of ETS exposure (CCR) found no association with asthma severity or pulmonary function but self-reported indicators did. It is unclear from the abstract which of the multiple pulmonary function measurements were used in the analysis. There was also no attempt to separate results for pre- and post-natal smoking.

Turkey: The Second Istanbul Study

Karadag et al. (2003) studied 32 children admitted to an emergency clinic with an acute asthma attack, 62.5% male. They ranged in age from 1 to 14 (mean 5.7 years). Urinary cotinine and creatinine levels were measured during and 4 weeks after the acute asthma attack. Comparing the period of the acute attack and the asymptomatic period, there was no significant difference in cotinine (295 vs 230 ng/ml), CCR (315 vs 204 ng/mg) or having a CCR above 30 ng/mg (81% vs 96%). It is not clear that the data from this study have been analysed correctly. It appears from the way the results are presented and the lack of reference to appropriate statistical tests that the analyses have been carried out as if two independent groups of 32 children are being compared, when tests should have been based on the distribution of within-subject differences, e.g. using a paired t-test. Whether this would have altered the significance of the difference between the time periods cannot be assessed.

Turkey: The Diyarbakir Study

Gürkan et al. (2000) studied hospital admissions retrospectively over a period of up to 4 years in 140 children with asthma aged 3-15 years, 65% male. Over the follow-up period 30 of the children (21.4%) had a mean of more than one admission per year and qualified as a multiple admission. Results relating multiple admissions to a range of factors were presented on an individual basis. These showed significant associations with both maternal smoking and smoking in the house, as summarized below:

		Multiple admissions		OR
		Yes	No	(95% CI)
Smoker in the house	Yes	16	34	2.55
	No	14	76	(1.12-5.82)
Maternal smoking	Yes	7	8	3.88[1]
	No	23	102	(1.28-11.8)

[1] Miscalculated as 4.05 (1.47-11.78) by the authors.

The authors also summarized the results of a multivariate logistic regression analysis in which only maternal smoking and age of the child were significant. They cited an adjusted OR of 3.25 (95% CI 1.13-8.85) for maternal smoking.

5.1.6. Description of the Studies – Other Areas

Kenya: The Nairobi Study

Wafula et al. (1999) studied 150 children with a history of wheezing with a mean age of 4 years (1 month - 10 years) with 60% male. The children were classified as having mild (32%), moderate (47%) or severe (21%) asthma, based on frequency of attacks. There was a non-significant tendency for passive smoke exposure at home to be associated with moderate asthma. Thus 36/71 children (51%) with moderate asthma were exposed to ETS as against 16/48 (33%) with mild asthma (OR 2.06, 95% CI 0.96-4.40). The definition of asthma used in this study required only *"at least two previous episodes of wheezing"* and seems very unrestrictive. It is also unexplained why passive smoking data were not presented for the severe cases. The only other risk factor considered in this study was breastfeeding and then not simultaneously with passive smoking.

New Zealand: The Christchurch Study

Fergusson & Horwood (1985) reported findings based on 1115 of an original 1265 children born in mid-1977 followed up to age 6 years. The relationship between parental smoking and respiratory illnesses during this period was studied. The authors presented the joint relationship of maternal and paternal smoking among the whole population to ever having had an asthmatic episode and to the rate of asthmatic attacks per 100 children. 134 children had a diagnosis of asthma or wheezy bronchitis, while 141 had a maternal report of an asthmatic attack. From these data we have estimated the annual rates per asthmatic child, separately for medical consultations and for maternal reports. The results show no apparent trend with paternal smoking, but some with maternal smoking, though it is impossible to assess statistical significance from the data provided.

	Source of	Smoking (cigs/day)		
Exposure	information on asthma	0	1-10	11+
Mother	Medical consultation	0.80	0.53	0.96
	Maternal report	1.59	0.96	2.03
Father	Medical consultation	0.82	0.64	0.85
	Maternal report	1.55	1.60	1.46

(Note that these data have been estimated by dividing the rate of attack per 100 children aged 0-6 by six times the risk per 100 children of having at least one episode by the age of 6 years. Strictly the rates per asthmatic child should be estimated during the period the child was asthmatic, but this cannot be done from the data available. Parental smoking was assessed on eight occasions, but it is unclear how parents who changed their smoking habits have been categorized.)

Nigeria: The Ibadan Study

Aderele (1982) studied 380 asthmatic children aged between 10 months and 13 years, with 62% male. 107 of the children had severe asthma, 87 had moderate asthma and 186 had mild disease. None of the children were known to be smokers. From the data presented one can calculate the following relative risk estimates (95% CI) for severe and moderate asthma compared to mild asthma.

Smoking by household members	Mild	Moderate	Severe
No	143	64	74
Adult	43	23	33
RR (95% CI)	1.00	1.20 (0.67-2.15)	1.48 (0.87-2.53)
Father and older siblings	20	16	27
RR (95% CI)	1.00	1.79 (0.87-3.67)	2.61 (1.37-4.96)
Other smoking (not father/siblings)	23	7	6
RR (95% CI)	1.00	0.68 (0.28-1.67)	0.50 (0.20-1.29)
Total	186	87	107

The author noted the significance ($p<0.01$) of the trend in relation to severity where the fathers and older siblings smoked, but did not discuss the implied negative relationship with severity in other households where there was a smoker. There was no adjustment for any confounding factors although data were collected on a wide variety of variables. The author also noted that 80 (34%) of the 234 children aged 5 years and above admitted they usually coughed on passively inhaling cigarette smoke.

South Africa: The Cape Town Study

Ehrlich et al. (2001) studied 249 children with asthma aged 6-11, 52% male, all of whom claimed never to have tried cigarettes, who underwent a test of bronchial responsiveness to histamine (or salbutamol if their FEV_1 was less than 75% of normal). In a multivariate analysis involving atopic history, baseline FEV_1, previous recognition of asthma by the parent, symptom score and medical insurance, a non-significant negative relationship was found between whether the chid responded to the test and mother's daily cigarettes, with the OR estimated as 0.97 (95% CI 0.67-1.41) for 1-14 cigs/day and 0.62 (0.34-1.11) for 15+ cigs/day. No significant associations were also found between bronchial responsiveness and other indices of parental smoking (current smoking or smoking in the first year of life by either parent individually, maternal smoking in pregnancy, number of smokers in the home or CCR). Nor was CCR related to the asthma symptom score. Baseline FEV_1, adjusted for age, sex and height, was also related to a variety of indices of smoking habits. There was no association with CCR. As shown in the table below, where selected results have been presented, there was a significant reduction in FEV_1 if the mother currently smoked or if both parents smoked, but a non-significant increase if the mother had ever smoked or if the father currently smoked.

The authors noted that *"the findings do not support a mechanism whereby ETS exposure aggravates existing childhood asthma by increasing BHR. This association may be masked, however, by the degree to which mothers of asthmatic children adjust their smoking. The results are consistent with an adverse effect of maternal smoking on lung function in asthmatic children."*

Exposure to smokers	Mean FEV_1, ml Exposed	Unexposed	Mean difference, ml (95% CI)	
Mother current	1409	1641	-232	(-461 to -2)
Mother ever	1526	1467	+59	(-107[1] to +225)
Mother in pregnancy	1464	1557	-93	(-296 to +110)
Father current	1561	1449	+112	(-78 to +302)
Mother and father	1385	1591	-150	(-286 to -131)[2]
Two or more in household	1455	1591	-137	(-366 to +92)

[1] Given as 107 in the source paper, but clearly erroneous and should be -107.

[2] There appears to be some error in the data presented for mother and father smoking. The estimate of -150 for the difference is not equal to the difference of the means (-206). Nor is it in the middle of the 95% CI. The width of the CI, 155, is also far too small given the SEs of 32 and 62 for the two means which imply a width almost twice this.

5.1.7. Summary of the Studies

Table 5.1 summarizes some details of the studies on ETS and asthma exacerbation in children. As noted earlier, there are a total of 60 publications, which together appear to relate to 47 studies, though in some cases this is not clear. The table is presented in chronological order of the first publication from the study. Later publications from a study are shown on the lines following the first publication, with the location and country columns left blank. Other data in the table (numbers of asthmatics, % male, age and "includes smokers") are shown for each of the multiple publications. In the distributions described below (which are study- rather than publication-based) the values used are those which are not given in parentheses. The value selected for a study is generally taken from the publication based on most asthmatic subjects or providing most information.

Publication date. The first study was published in 1974, with two studies published in 1980-1984, five in 1985-1989, five in 1990-1994, 12 in 1995-1999 and 22 in 2000-2004. The steeply increasing publication rate is evident.

Location. Twenty-two studies have been conducted in North America, 18 in the USA and four in Canada. Thirteen studies have been conducted in Europe in a total of 10 countries, with no more than two from any country. Three studies have been in Turkey, two in the Middle East, three in India or the Far East, three in Africa and one in New Zealand. In all, studies have been conducted in 22 different countries. This represents quite an extensive geographical coverage, though no studies have been reported from Central or South America.

Most of the studies have been conducted in specific cities or areas, though results have been reported for two nationwide studies in the USA and one in France. One study in Canada was based on nine regions.

Number of asthmatic subjects. Based on the publication that considered the largest number of asthmatic subjects, the smallest study involved only 17 asthmatic subjects, while the largest is the nine region study in Canada (Dales et al., 2002) involving 3010. The median study size is 167. The distribution of study size is as follows:

Study size	17-50	51-100	101-250	251-500	501-1000	1001-3010
Studies	8	7	18	6	7	1

Table 5.1. Some details of the exacerbation studies in children

Publication[1]	Location[2]	Country[2]	Number of asthmatics[3]	% male[3,4]	Age[3,5]	Includes smokers[3,6]
O'Connell & Logan, 1974	Minnesota	USA	35[7]	60	2-16	NK
Aderele, 1982	Ibadan	Nigeria	380	62	1-13	No
Gortmaker et al., 1982	Michigan and Massachusetts	USA	217	NK	0-17	NK
Fergusson & Horwood, 1985	Christchurch	New Zealand	141[8]	NK	0-6	NK
Murray & Morrison, 1986	Vancouver	Canada	(94)	(65)	(7-17)	(2)
Murray & Morrison, 1988			(240)	(68)	(7-17)	(No)
Murray & Morrison, 1989			(414)	70	(1-17)	(No)
Murray & Morrison, 1992			(240)	(NK)	(7-17)	(No)
Murray & Morrison, 1993			807	(NK)	1-17	No
Evans et al., 1987	New York	USA	191	60	4-17	No
O'Connor et al., 1987	Boston	USA	21	62	5-9	No
Martinez et al., 1988	Viterbo	Italy	22	NK	9	NK
Weitzman et al., 1990b	Nationwide	USA	117	NK	0-5	NK
Weitzman et al., 1990a			(110)	63	(2-5)	(NK)
Lilienfeld et al., 1990*	New York	USA	(107)	(NK)	(3-14)	(NK)
Ehrlich et al., 1992			107	62	3-14	No
Frischer et al., 1992	Freiburg	Germany	171	NK	mn7.3	NK
Frischer et al., 1993			(113)	(NK)	(md7.3)	(NK)
Meinert et al., 1994			(162)	(NK)	(8)	(NK)
Salmun et al., 1992*	Portland	USA	(199)	(NK)	(0-13)	(NK)
Chilmonczyk et al., 1993			199	72	0-13	NK
Ogborn et al., 1994	Baltimore	USA	56	57	3-11	NK
Abulhosn et al., 1995*	Seattle	USA	(22)	(NK)	(2-9)	(NK)

Table 5.1. Continued

Publication[1]	Location[2]	Country[2]	Number of asthmatics[3]	% male[3,4]	Age[3,5]	Includes smokers[3,6]
Abulhosn et al., 1997			22	41	2-13	NK
Chan & Chen, 1995*	Taiwan	Taiwan	46	NK	NK	NK
LeSon & Gershwin, 1995	Davis	USA	300	55	5-12	NK
Strachan & Carey, 1995	Sheffield	England	486	NK	12-18	NK
MacArthur et al., 1996	Toronto	Canada	68	71	md3	NK
Meijer et al., 1996	Zwolle	Netherlands	55	60	mn9.3	NK
Callén Blecua et al., 1997	San Sebastian	Spain	312	NK	3-19	1
Hu et al., 1997	Chicago	USA	167	51	10-11[9]	5%[10]
Seidler et al., 1998	Lower Saxony	Germany	200	65	0-8	NK
Dubus et al., 1998	Marseilles	France	(46)	(57)	(5-14)	No
Oddoze et al., 1999			90	60	4-14	(NK)
Shamssain & Shamsian, 1999	N.E.England	England	685[11]	59	6-7	NK
Wafula et al., 1999	Nairobi	Kenya	150	60	0-10	NK
Al-Ghamdy et al., 2000	Al-Majmaah	Saudi Arabia	606	69	<13[12]	NK
El-Dahr et al., 2000*	New Orleans	USA	17	56	6-16	No
Güler et al., 2000*	Istanbul	Turkey	47	68	5-15	NK
Gürkan et al., 2000	Diyarbakir	Turkey	140	65	3-15	NK
Li et al., 2000	S.California	USA	749	59	7-19	13
Melén et al., 2000*	Stockholm	Sweden	(144)	(NK)	(1-6)	(NK)
Melén et al., 2001			181	76	1-6	NK
Ratageri et al., 2000	New Delhi	India	120	72	5-15	NK
Schwartz et al., 2000	Kuopio	Finland	74	61	7-12	NK
Crombie et al., 2001	Tayside and Fife	Scotland	438	66	2-12	NK
Ehrlich et al., 2001	Cape Town	South Africa	249	52	6-11	No
Mayo, 2001	Edmonton	Canada	62	55	1-9	NK
Venners et al., 2001	Anqing	China	529	50	8-15	Never

Table 5.1. Continued

Wilson et al., 2001b	California	USA	87	51	3-12	NK
Dales et al., 2002	9 regions	Canada	3010	52	5-19	NK
Gaspar et al., 2002	Lisbon	Portugal	248	57	1-10	NK
Kalaajieh, 2002	Tripoli	Lebanon	288	64	6-15	NK
Mannino et al., 2002	Nationwide	USA	523	59	4-16	No
Chapman et al., 2003			(309)	(60)	(8-16)	Never[13]
Morkjaroenpong et al., 2002	Baltimore and Washington DC	USA	590	40	5-11	NK
Wamboldt et al., 2002	Denver	USA	152	57	7-18	No[14]
Karadag et al., 2003	Istanbul	Turkey	32	63	1-14	NK
Soussan et al., 2003	Nationwide	France	167	64	6-12	NK
Halterman et al., 2004	Rochester, NY	USA	184	63	3-7	NK

[1] Publications marked with an asterisk are abstracts.
[2] Where there are multiple publications from the same study, the publications are shown together in the table with the location and country shown only for the earliest.
[3] Where there are multiple publications from the same study, the value shown not in brackets is that used for the distributions discussed in the text.
[4] NK = not known.
[5] Age range is shown if available, otherwise mean preceded by mn, or median preceded by md.
[6] NK = not known, No = no current smokers, Never = no ever smokers, number = number of known smokers included in analysis.
[7] In follow-up phase. Selected from 400 asthmatics.
[8] 141 with a maternal report of an asthmatic attack, 134 with a diagnosis of asthma or wheezy bronchitis.
[9] 96% were aged 10-11.
[10] 5% of all children, not of all asthmatic children, were smokers.
[11] Approximate estimate.
[12] 48% were aged <1.
[13] Never or <5 packs during life.
[14] Children were asked if they smoked, but the number who did was not stated.

Sex of subjects. All studies either included both sexes, or did not state the sex of the subjects. Generally, there were more boys than girls, with the percentage of boys up to 76% (Table 5.1). Exceptions were the studies in Baltimore (Morkjaroenpong et al., 2002) and Seattle (Abulhosn et al., 1997) with about 40% boys.

Age of subjects. Table 5.1 shows the age range of the subjects where available or, except for one study where no information on age was provided, the mean or median age. Of the 43 studies that provided age range data, the number of studies where the range covered specific ages is as follows:

Age	0	1	2	3	4	5	6	7	8	9
Studies	7	13	16	22	25	31	35	36	35	35
Age	10	11	12	13	14	15	16	17	18	19
Studies	33	31	28	23	19	16	11	8	5	3

It can be seen that age 7 was the most commonly studied, with over 30 of the 43 studies providing data for ages in the range 5 to 11. The number of studies including infants (aged 0-1) or young adults (aged 16-19) was considerably less. The mean number of ages covered by the studies was 10, so it is clear that the tendency was not to concentrate on a very limited age range, though some studies did.

Smoking habits. For 33 of the 47 studies (70%) no mention was made of smoking by the child, though some were based on children so young that smoking could effectively be ruled out. For one study, attention was restricted to children reported never to have smoked (Venners et al., 2001) and one publication from NHANES III (Chapman et al., 2003) was restricted to children with a lifetime consumption of 5 packs at most. In another analysis from NHANES III (Mannino et al., 2002) and in nine other studies (indicated by "No" in the final column in Table 5.1) current smokers were excluded. In three studies, and in an early analysis from the Vancouver study (Murray & Morrison, 1986), a few smokers were included in the analysis. The largest proportion of smokers was the 5% of all subjects in the study reported by Hu et al. (1997), although the proportion of smokers among the asthmatics was unknown.

Study design and subject selection. Table 5.2 summarizes details of the study design and subject selection for the 47 studies of asthma exacerbation in children. The majority of the studies fall into two broad classes, studies of asthma *cases* identified through medical records, and *cross-sectional* studies of children generally with the classification of asthma being based on questionnaire. There are 24 studies in the first class, of which 9 included an element of follow-up. For some of these studies the cases had been identified from a previous cross-sectional study or cohort study, or were part of a case-control study. There are 13 studies in the second class, 8 involving surveys in schools (one with follow-up) and 5 surveys in the general population.

There are five rarer study designs:

- One *cohort* study (Fergusson & Horwood, 1985) which followed children from birth to 6 years with repeated questionnaires used to identify asthmatics;
- Three *case-control* studies (Ehrlich et al., 1992; Ratageri et al., 2000; Gaspar et al., 2002) which compared groups of cases with differing asthma presentation (acute vs non-acute or mild vs severe);
- Two *within-person* studies (Ogborn et al., 1994; Karadag et al., 2003) in which children were compared while having an acute attack and later, when symptom-free;
- Three *intervention* studies (El-Dahr et al., 2000; Wilson et al., 2001b; Halterman et al., 2004) which investigated effects of advice to reduce ETS exposure or of school-based provision of medication; and
- One *experimental* study (Meijer et al., 1996) which investigated effects of treatment withdrawal.

Apart from giving information on broad study design, Table 5.2 makes clear the wide variety of definitions of asthma used in the studies, whether based on questionnaire or on medical records.

Markers of exposure. Table 5.3 shows for each study whether data are available by ETS exposure, by a cotinine-based marker or by exposure during gestation, as well as giving details of the actual exposure indices used. Of the 47 studies, all but three (marked by a dash in the relevant column) reported results for an index of ETS exposure. Although a few of the studies presented results specifically relating to maternal smoking, most considered smoking by other household members, including the father. Relatively few considered exposure outside the home, such as at day care (Chilmonczyk et al., 1993) or in all locations (Ogborn et al., 1994). Rather more studies took into account not only whether household members smoke, but also whether the smoking occurred inside the home. Eight studies reported results for a cotinine based marker, in most cases based on urine samples, though one study reported results based on saliva cotinine (Crombie et al., 2001) and one on serum cotinine (Mannino et al., 2002).

Adjustment for potential confounding variables. Of the 47 studies, 23 (49%) did not adjust for any potential confounding variables at all, not even age.

One of these (Ogborn et al., 1994) was a study of changes within child, where adjustment was not relevant. There were also some studies where the groups being compared were noted to be similar in respect of certain variables – such as sex, age, ethnicity and SES (Ehrlich et al., 1992); sex, age and asthma severity (Abulhosn et al., 1997); or body mass index (Dubus et al., 1998) – but in most of these the issues of confounding by other variables had not been addressed at all.

Table 5.4 gives details of the potential confounding variables taken into account in the different studies. Where a variable is listed for a study, it was taken into account in some of the relevant analyses, though not necessarily in all. Variables indicated in parentheses were considered as potential confounders but found to make little difference, with the analyses presented not actually adjusting for them.

Of the 24 studies listed, two (Martinez et al., 1988; Frischer et al., 1992) involved children of such a limited age range that age adjustment was not needed, and one was a study of changes within child (Wilson et al., 2001b). Of the other 21, only five (Gortmaker et al., 1982; Evans et al., 1987; Ratageri et al., 2000; Gaspar et al., 2002; Halterman et al., 2004) apparently ignored age.

Of the 23 between-child comparison studies considered in Table 5.4, 14 considered the sex of the child, with 10 actually presenting results adjusted for it.

There are a wide variety of other factors taken into account in at least one study. The broad types of variables considered most commonly, with the number of studies adjusting for them (or determining that they did not have a material confounding effect) are as follows: child's medical history (18), family medical history or parental age (12), socio-economic status (SES) or parental education (9), height, weight or BMI (6), pets (5), location (including urban/rural) (5), family composition (4), and child's education or day care (4).

Not included among the variables listed in Table 5.4 are indices of ETS exposure. A few studies presented analyses linking an endpoint of interest to one index of ETS exposure, while adjusting for another (O'Connor et al., 1987; Murray & Morrison, 1988; Murray & Morrison, 1989; Frischer et al., 1992; Crombie et al., 2001).

Table 5.2. Details of study design and subject selection for the exacerbation studies in children

Publication[1]	Study type	Identification of asthma cases
O'Connell & Logan, 1974	Cases followed for 6 mo to 2 yr	Random from clinic files, children affected by ETS followed
Aderele, 1982	Case	Consecutive cases at asthma clinic
Gortmaker et al., 1982	Population cross-sectional	Questionnaire (ever had asthma)
Fergusson & Horwood, 1985	Cohort – from birth to 6 yrs	Repeated questionnaire (physician diagnosis of asthma/wheezy bronchitis; maternal report of attack)
Murray & Morrison, 1986, Murray & Morrison, 1988, Murray & Morrison, 1989, Murray & Morrison, 1992, Murray & Morrison, 1993	Case	Consecutive referrals at allergy clinic
Evans et al., 1987	Case	From outpatient clinics
O'Connor et al., 1987	School cross-sectional, including all household members	Questionnaire (told by physician has asthma in last 12 months)
Martinez et al., 1988	School cross-sectional	Questionnaire (ever had asthma)
Weitzman et al., 1990b, Weitzman et al., 1990a	Population cross-sectional	Questionnaire (has asthma, had it for 3 months, not cured)
Lilienfeld et al., 1990, Ehrlich et al., 1992	Case-control	Acute: ER; non-acute: asthma clinic
Frischer et al., 1992, Frischer et al., 1993, Meinert et al., 1994	School cross-sectional	Questionnaire (physician-diagnosis of asthma or wheezy bronchitis)
Salmun et al., 1992, Chilmonczyk et al., 1993	Case	Routine visit to allergy asthma clinic
Ogborn et al., 1994	Within subject comparison during acute episode and when symptom-free 3-4 wks later	ER visit with acute asthma attack
Abulhosn et al., 1995, Abulhosn et al., 1997	Cases followed for 1 mo	All admissions with asthma diagnosis only
Chan & Chen, 1995	Cases monitored for 6 mo	Not known

Table 5.2. Continued

Publication[1]	Study type	Identification of asthma cases
LeSon & Gershwin, 1995	Case	Asthma admission to tertiary-care medical centre
Strachan & Carey, 1995	Case-control (drawn from school cross-sectional, only cases relevant)	Questionnaire (12+ wheezing attacks, or an attack that limited speech, in last 12 months)
MacArthur et al., 1996	Cases followed for 12 mo	Two admissions to hospital within 12 mo (follow-up period starts at second admission)
Meijer et al., 1996	Experimental, of treatment withdrawal	Symptoms of asthma, increased total IgE and allergy to HDM but not others, FEV>70% and increased bronchial responsiveness. Recruited at school (no details)
Callén Blecua et al., 1997	Case	First visit to outpatient clinic
Hu et al., 1997	Population cross-sectional	Questionnaire (ever physician diagnosed asthma)
Seidler et al., 1998	Cases followed for 3 yr	Any contact with participating doctor in 6 month baseline phase and any contact with same doctor in 6 months follow-up phase
Dubus et al., 1998, Oddoze et al., 1999	Case	Referred to respiratory function laboratory
Shamssain & Shamsian, 1999	School cross-sectional	Questionnaire (ever had asthma)
Wafula et al., 1999	Case	Consecutive cases at clinic or ward with 2+ previous episodes of wheezing
Al-Ghamdy et al., 2000	Case	Consecutive cases at health care centres and clinics
El-Dahr et al., 2000	Intervention trial on cases of effect of cessation advice	Not known
Güler et al., 2000	Cases, followed for 1 yr	Not known
Gürkan et al., 2000	Cases (studied retrospectively for 13 mo – 4 yrs)	All first admissions for asthma during 3 yr period
Li et al., 2000	Population cross-sectional	Questionnaire (physician diagnosed asthma)
Melén et al., 2000, Melén et al., 2001	Cases followed for 2 yrs	Referred to paediatric clinics
Ratageri et al., 2000	Case-control (only cases relevant)	Consecutive cases with severe or mild asthma at clinic of tertiary hospital

Schwartz et al., 2000	School cross-sectional (3 mo diary study)	Questionnaire (ever doctor-diagnosed asthma, or wheezing or shortness of breath with wheezing in last 12 mo)
Crombie et al., 2001	Case	From GP record (and previously took part in intervention trial of advice to reduce ETS)
Ehrlich et al., 2001	Case (drawn from school cross-sectional study)	Questionnaire (parent-reported asthma and 1+ symptom last 12 mo, or 4+ symptoms last 12 mo)
Mayo, 2001	Case	Admitted with acute exacerbation without infection
Venners et al., 2001	Case	Physician diagnosed (had to have at least one sibling and 0 or 1 parents with asthma)
Wilson et al., 2001b	Intervention trial on cases of advice to reduce ETS	Visited ER or urgent clinic or hospitalised for acute asthma in last yr, and ETS exposed
Dales et al., 2002	Cases (drawn from school cross-sectional study)	Questionnaire (ever physician-diagnosed asthma and symptoms, attack or medication in last 12 mo)
Gaspar et al., 2002	Case-control	All acute asthma ER admissions and matched outpatient cases
Kalaajieh, 2002	Cases followed for up to 8 yr	All acute ER admissions
Mannino et al., 2002, Chapman et al., 2003	Population cross-sectional	Questionnaire (ever physician diagnosed asthma)
Morkjaroenpong et al., 2002	Case	All children with asthma diagnosis on school health records
Wamboldt et al., 2002	Cases (drawn from cohort study)	From school (receiving daily medication) or from insurance records (medication in last 6 mo or visit to allergist in last yr) but excluding 6+ steroid bursts or 2+ hospitalisations in last yr, or ever intubated
Karadag et al., 2003	Comparison during acute episode and when symptom-free 4 wks later	Consecutive admissions to emergency clinic with acute asthma
Soussan et al., 2003	Cases with 3 yr follow-up	First two cases of recently diagnosed asthma (excluding severe cases) at each chest specialist in France, and on anti-inflammatory medication at 12 mo follow-up
Halterman et al., 2004	Intervention trial on cases of school-based provision of medication	All children with 2+ symptom days/wk, 2+ symptom nights/mo, 3+ acute visits in last yr or 1+ hospitalisation in last yr identified from school medical records.

ER = Emergency room or department

[1] Multiple publications from the same study are separated by commas.

Table 5.3. Indices of smoke exposure for which results are reported for the exacerbation studies in children

Publication[1]	Index of ETS exposure	Cotinine	Exposure during gestation
O'Connell & Logan, 1974	Parents quit or continued	-	-
Aderele, 1982	Household members smoke regularly	-	-
Gortmaker et al., 1982	Mother smokes	-	-
Fergusson & Horwood, 1985	Parents smoke	-	-
Murray & Morrison, 1986, 1988, 1989, 1992, 1993	Parents smoke	-	-
Evans et al., 1987	Household members smoke	-	-
O'Connor et al., 1987	Parents smoke	-	-
Martinez et al., 1988	Parents smoke	-	-
Weitzman et al., 1990b, 1990a	-		Mother
Lilienfeld et al., 1990, Ehrlich et al., 1992	Household members smoke	Urine CCR	-
Frischer et al., 1992, 1993, Meinert et al., 1994	Mother, Father smokes[2]	-	-
Salmun et al., 1992, Chilmonczyk et al., 1993	Household or day care smoking	Urine CCR	-
Ogborn et al., 1994	ETS in any location in last 48 hours	Urine cotinine, CCR	-
Abulhosn et al., 1995, 1997	Parents smoke	-	-
Chan & Chen, 1995	-	Urine CCR	-
LeSon & Gershwin, 1995	Parents, family, room-mates smoke	-	-
Strachan & Carey, 1995	Parents smoke (at home)	-	Mother[3]
MacArthur et al., 1996	Household members smoke	-	-
Meijer et al., 1996	Parents smoke	-	-
Callén Blecua et al., 1997	Parents smoke	-	-
Hu et al., 1997	Mother smokes	-	Mother
Seidler et al., 1998	Parents smoke (at home)	-	-
Dubus et al., 1998, Oddoze et al., 1999	Parents smoke[4]	Urine cotinine, CCR[4]	-
Shamssain & Shamsian, 1999	Parents smoke	-	-
Wafula et al., 1999	Household ETS	-	-
Al-Ghamdy et al., 2000	Parents smoke	-	-
El-Dahr et al., 2000	Parents smoking normally then reducing	-	-

Güler et al., 2000	Parents smoke	-	Mother[5]
Gürkan et al., 2000	Mother smokes, Indoor smoking (at home)	-	-
Li et al., 2000	Mother smokes	-	Mother
Melén et al., 2000, 2001	Parents smoke	-	-
Ratageri et al., 2000	Family members smoke	-	-
Schwartz et al., 2000	Smokers at home	-	-
Crombie et al., 2001	Parents smoke	Saliva cotinine	-
Ehrlich et al., 2001	Parents smoke	-	Mother[6]
Mayo, 2001	Parents 1+ pack/day	-	-
Venners et al., 2001	Father smokes[7]	-	-
Wilson et al., 2001b	Intervention vs usual care	-	-
Dales et al., 2002	Regular ETS at home	-	-
Gaspar et al., 2002	Household smoking	-	-
Kalaajieh, 2002	-	-	Household[8]
Mannino et al., 2002, Chapman et al., 2003	Smokers at home	Serum cotinine[9]	-
Morkjaroenpong et al., 2002	Caregiver smokes at home[10]	-	-
Wamboldt et al., 2002	Household members smoke	-	-
Karadag et al., 2003	Household members smoke	Urine cotinine	-
Soussan et al., 2003	Household members smoke (at home)	-	-
Halterman et al., 2004	Smokers at home	-	-

[1] Multiple publications from the same study are separated by commas.
[2] Results for father smoking only reported in Frischer et al., 1993.
[3] Around time of birth.
[4] Parental smoking and urinary CCR results only reported in Oddoze et al., 1999.
[5] Also passive smoking by mother in pregnancy.
[6] Also results relating to mother ever smoked and parents smoked in child's first year.
[7] Mothers all never smokers and ex-smoking fathers excluded.
[8] At birth.
[9] Household smoking results only used in Chapman et al., 2003; cotinine results only reported in Mannino et al., 2002.
[10] Caregivers who smoke, but not at home, excluded.

Table 5.4. Potential confounding variables taken into account in the exacerbation studies in children

Publication	Age[1]	Sex[1]	Others[1,2]
Gortmaker et al., 1982	No	No	Sample (= urban/rural)
Murray & Morrison, 1986, 1988, 1989, 1992, 1993	Yes	Yes	Recent respiratory infection, recent medication, positive skin test, family history of asthma, hot air heating, wood stove, gas range, pets, duration of asthma, age of onset of asthma, number of siblings, atopic dermatitis
Evans et al., 1987	No	No	Days with asthma symptoms per month
O'Connor et al., 1987	(Yes)	(Yes)	History of cold in last two weeks, predicted FEV, (height, atopy)
Martinez et al., 1988	All 9	Yes	Atopy
Frischer et al., 1992, 1993, Meinert et al., 1994	All 7-8	Yes	Prematurity, pneumonia in first year, atopy, education
Chilmonczyk et al., 1993	Yes	Yes	Day-care attendance, mother's age and education
Meijer et al., 1996	Yes	No	Pets, HDM exposure, PC_{20}
Seidler et al., 1998	Yes	Yes	Parental education, frequency of asthmatic episodes, infection-associated asthma, asthma on exertion, neurodermitis, hospitalisation, speciality of treating physician, parental asthma, sensitivity to exhaust gases, region
Gürkan et al., 2000	Yes	(Yes)	(Allergic conjunctivitis, eczema, frequent URI, familial allergy, +ve SPT, IgE, urban residency, using inhaled steroids)
Li et al., 2000	Yes	No	Community, school grade, spirometer, pressure, technician, height, race
Melén et al., 2000, 2001	Yes	No	Heredity, cat, dog, window condensation, 3+ SPT (possibly cat allergen, IgE cat, but not clear if univariate or multivariate)
Ratageri et al., 2000	No	No	Age of onset, past history lung disease, family history asthma, allergy, breastfeeding, overcrowding, pets, cooking, worm infestation, eosinophil count, air pollution
Schwartz et al., 2000	Yes	Yes	Height, weight, atopy, father's education, medication, day of study, weekend, temperature, humidity
Crombie et al., 2001	Yes	(Yes)	Severity of asthma perceived and based on treatment step, number of children in family (parental age)

Table 5.4. (continued)

Publication	Age[1]	Sex[1]	Others[1,2]
Ehrlich et al., 2001	Yes	Yes	Height, atopy, baseline FEV_1, asthma group, symptom score, medical insurance (parental education, mother contributes to income, hay fever, eczema, familial asthma)
Venners et al., 2001	Yes	No	Height, weight, father's education
Wilson et al., 2001b	No[3]	No[3]	Baseline outcome
Gaspar et al., 2002	No	No	Prior asthma hospitalisation, atopy, maternal asthma, last year asthma admission, onset of symptoms before 12 mo, attendance at day care or kindergarten, family size
Kalaajieh, 2002	(Yes)	(Yes)	Respiratory infections (atopic dermatitis, allergic rhinitis, IgE, eosinophil)
Mannino et al., 2002, Chapman et al., 2003	Yes	Yes	Race/ethnicity, SES, family size, parental history asthma, sitting height, parental history allergy or asthma, height, body mass, skinfold thickness, gas stove, income, pets, physical activity
Morkjaroenpong et al., 2002	Yes	No	Caregiver education, asthma primary care, medication
Soussan et al., 2003	Yes	Yes	Father's occupation, atopy, sensitisation to mites, cats/dogs, pollen and mould, perennial asthma, perennial/seasonal allergic rhinitis, atopic dermatitis, asthma in father, mother and sibs, gas cooking, mould, cat, dog, carpet, mattress type, medication compliance.
Halterman et al., 2004	No	(Yes)	(Baseline severity, baseline medication, race, ethnicity, parental age, parental education, poverty)

[1] Variables which were considered, found not to have any material confounding effect, but not adjusted for in any analysis are indicated by parentheses.

[2] The list of other variables considered is that taken into account in at least some relevant analysis. Not all analyses necessarily considered all of them.

[3] Within-child study so not necessary to adjust.

5.2. RESULTS

5.2.1. Asthma Exacerbation and Severity

A wide variety of indices of asthma exacerbation and severity have been used. These have been classified into nine groups, with results presented in Tables 5.5 to 5.13.

The layout of each table is similar, with columns for publication, endpoint, exposure and result. In the simplest case there is a single endpoint and single exposure with the result usually expressed as an OR comparing the exposed and unexposed or as means for the exposed and unexposed. In some cases the comparison is different, e.g. highest vs lowest cotinine group, but this is made clear in the tables. Where results are given by level of endpoint (e.g. mild, moderate, severe asthma) or by level of exposure (e.g. 0, 1-9, 10+ cigs/day by the mother) the results are presented relative to a defined comparison (base) group. Where 95% confidence intervals are not available, p values are presented as $p<0.001$, $p<0.01$, $p<0.05$ or NS ($p\geq0.05$).

Each table in general presents a single set of results per study. Where there are multiple publications from the same study, the results selected are generally those based on the largest number of subjects, with data given in papers preferred to data given in abstracts.

Hospitalisation: Table 5.5

Nine studies have related hospital admissions, or in one study (Dales et al., 2002) hospitalisations or emergency department visits, to ETS exposure. Four of these (Gürkan et al., 2000; Mayo, 2001; Kalaajieh, 2002; Dales et al., 2002) reported a significant increase in frequency or length of admissions in relation to parental smoking or other indices of ETS exposure at home. A non-significant positive association was also seen in another study (MacArthur et al., 1996). Of the remaining four studies, two (Evans et al., 1987; Halterman et al., 2004) reported no significant association, but in fact provided little useful information, and one (Wilson et al., 2001b) reported a non-significant reduction in hospitalisation in the intervention group, which did not actually show any clear reduction in ETS exposure relative to the usual care group. The final study (Mannino et al., 2002) reported a significantly *reduced* risk of hospitalisation for asthma in children with the highest cotinine levels. The authors considered that this negative association might have been because parents altered their smoking habits as a result of the hospitalisation, but this seems somewhat speculative. Their study generally found a tendency for cotinine to be positively associated with other asthma severity outcomes, and other studies, such as Dales et al., 2002, reported a positive association between current ETS exposure and previous hospitalisation. The explanation for this aberrant result, which conflicts with the general tendency of a positive relationship is unclear. However, as it was quite highly significant (OR = 0.2, 95% CI 0.1-0.5) and based on a nationally representative US sample from NHANES III, it should not be lightly dismissed.

Only one study (Weitzman et al., 1990b) reported findings for maternal smoking in pregnancy. This found that the mean number of overnight hospitalisations (from any cause) was unrelated to the number of cigarettes smoked by the mother (1.1, 1.3 and 1.0 for 0, 1-9 and 10+ cigs/day).

Table 5.5. Summary of results for children relating hospitalisation to ETS exposure

Publication	Endpoint	Exposure	Result[1]
Evans et al., 1987	Hospitalisation for asthma in last year	Household member smokes	Not significant (data not shown)
MacArthur et al., 1996	Readmission for asthma within a year	Household member smokes	OR 1.44 (0.87-2.37)
Gürkan et al., 2000	Multiple admissions per year	Mother smokes	OR 3.25 (1.13-8.85)[2]
		Indoor smoking at home	OR 2.55 (1.12-5.82)[3]
Mayo, 2001	Duration of stay for asthma	Parent(s) smoke 1+ pack/day	Mean 4.35 vs 2.86 days ($p<0.05$)
Wilson et al., 2001b	Hospitalisation for asthma in year	Intervention effect	OR 0.34 (NS)[4]
Dales et al., 2002	Hospitalisation for asthma or ER visit in last year	Regular ETS at home	OR 1.55 (1.22-1.97)
Kalaajieh, 2002	Multiple admissions for asthma per year	Mother smokes (at birth)	OR 6.10 (2.98-12.55)[5]
		Indoor smoking (at birth)	OR 3.06 (1.81-5.18)
Mannino et al., 2002	Hospitalisation for asthma in last year	Highest vs lowest cotinine[6]	OR 0.2 (0.1-0.5)[7]
		Intermediate vs lowest cotinine	OR similar to that for highest vs lowest, but NS
Halterman et al., 2004	Hospitalisation for asthma in study year	Smokers in home	OR 0.63 (0.15-2.58)

[1] Unadjusted for covariates except where stated.

[2] Adjusted for age (for mother smokes result only).

[3] Indoor smoking found to be non-significant in multiple logistic regression analysis with maternal smoking already included in the model.

[4] Intervention vs control, with adjustment for baseline differences.

[5] OR for maternal smoking noted to be significant ($p<0.001$) in multiple logistic regression analysis, with recurrent URI the only other factor included, but OR not given.

[6] Serum cotinine groups are 0.050 to 0.115 ng/ml = low, 0.116 to 0.639 ng/ml = intermediate, and 0.640 to 20 ng/ml = high.

[7] Adjusted for age, race/ethnicity, SES, family size and parental history of asthma.

Emergency Room Visits: Table 5.6

Six studies have considered emergency room visits, urgent consultations or other related endpoints. Four of these also reported results for hospitalisations (Table 5.5), and for one of them (Dales et al., 2002) the data, for hospitalisations or emergency department visits, are the same as presented there. Three of the studies (Evans et al., 1987; LeSon & Gershwin, 1995; Dales et al., 2002) reported a significant positive association with ETS exposure, the most striking of which was the hugely strong relationship with whether the admission requires intubation (LeSon & Gershwin, 1995). A further study (Wilson et al., 2001b) also reported a significant reduction in acute medical visits in the intervention group though, as noted above, it was not clear if that group had in fact reduced ETS exposure. Other studies (Hu et al., 1997; Halterman et al., 2004) reported no significant association. In total, however, the data provide evidence of an association of emergency room visits with ETS exposure.

Only one study (Hu et al., 1997) has reported results for maternal smoking in pregnancy, finding no association.

Table 5.6. Summary of results in children relating emergency room visits and urgent consultations to ETS exposure

Publication	Endpoint	Exposure	Result[1]
Evans et al., 1987	ER visits for asthma in last year	Household member smokes	Mean 3.46 vs 2.12 ($p<0.01$)[2]
LeSon & Gershwin, 1995	Asthma admission requires intubation	ETS from parents, family members or room mates	OR 22.4 (7.4-68.0)[3]
Hu et al., 1997	ER visit for asthma in last year	Mother smoked in last week	OR 0.86 (0.40-1.89)
Wilson et al., 2001b	More than one acute medical visit for asthma in last year	Intervention effect	OR 0.32 ($p<0.05$)[4]
Dales et al., 2002	Hospitalisation for asthma or ER visit in last year	Regular ETS at home	OR 1.55 (1.22-1.97)
Halterman et al., 2004	3+ acute visits for asthma in study year	Smokers in home	OR 1.23 (0.62-2.43)

ER = emergency room or department

1 Unadjusted for covariates except where stated.

2 Adjusted for days with asthma symptoms per month.

3 From the data presented we estimate OR 22.2 (4.8-102.9).

4 Intervention vs control, with adjustment for baseline difference.

Restricted activity: Table 5.7

Six studies have related indices of restricted activity to ETS exposure. No significant association was reported in four studies (Gortmaker et al., 1982; Wilson et al., 2001b; Mannino et al., 2002; Morkjaroenpong et al., 2002). However one study (Halterman et al., 2004) reported significantly more school absences where there were smokers in the home, and another (El-Dahr et al., 2000) reported that the child had significantly more days with restricted activity during the three month period where the parents were smoking normally

than during the following three month period after encouragement to quit smoking. The design of the latter study, reported only as an abstract, does not include a valid control group. The data for restricted activity, taken as a whole, do not demonstrate the existence of an association with ETS exposure.

No data are available relating restricted activity to exposure during gestation.

Table 5.7. Summary of results for children relating restricted activity to ETS exposure

Publication	Endpoint	Exposure	Result[1]
Gortmaker et al., 1982	Functional impairment[2]	Mother smokes cigarettes	OR 1.43 (0.79-2.65)[3]
El-Dahr et al., 2000	% days with restricted activity	Parent smoking normally, then reducing	10% vs 5% ($p<0.05$)
Wilson et al., 2001b	% with activity limitation in 2 wks before interview	Intervention effect	OR 0.64 (NS)[4]
Mannino et al., 2002	6+ school absences in last year	Highest vs lowest cotinine[5] Intermediate vs lowest cotinine	OR 1.8 (0.9-3.6) OR similar to that for highest vs lowest, and NS
Morkjaroen-pong et al., 2002	Limited physical activity because of asthma in past 6 months	ETS exposure from caregiver: 0 cigs/day (base) 1-9 cigs/day 10+ cigs/day Any	OR 1.00 0.57 (0.35-0.93) 1.03 (0.60-1.77) 0.74 (0.50-1.10)
	School days missed because of asthma in past 6 months	ETS exposure from caregiver: 0 cigs/day (base) 1-9 cigs/day 10+ cigs/day Any	Mean 6.7 6.2 (NS) 8.4 (NS) 7.2 (NS)
Halterman et al., 2004	School absences because of asthma during study year	Smokers in home	Mean 10.28 vs 5.92 ($p<0.01$)

[1] Unadjusted for covariates except where stated.

[2] Functional impairment = affects ability to attend school or do any of the things a child of that age usually does.

[3] Adjusted for study sample (= urban/rural).

[4] Intervention vs control, with adjustment for baseline difference.

[5] Serum cotinine groups are 0.050 to 0.115 ng/ml = low, 0.116 to 0.639 ng/ml = intermediate, and 0.640 to 20 ng/ml = high.

Acute and Non-Acute Asthma: Table 5.8

Two studies (Ogborn et al., 1994; Karadag et al., 2003) have compared ETS exposure in children at a time when they had an acute asthma attack and a few weeks later when they were well. Neither of these studies reported any significant increase in cotinine during the acute period, though one study (Ogborn et al., 1994) reported significantly increased reported ETS exposure based on one index, but not others. There were also two studies of case-control design (Ehrlich et al., 1992; Gaspar et al., 2002), where the cases were acute asthmatics and the controls non-acute asthmatics. The first of these reported no evidence of an association, but the second reported significant associations with various indices of ETS exposure, the strongest being the OR of 6.63 (2.5-17.8) for any ETS exposure. The overall data do not show a clear difference in ETS exposure between acutely and non-acutely asthmatic children.

No data were available relating acute and non-acute asthma to exposure during gestation.

Table 5.8. Summary of results comparing ETS exposure in acute and non-acute asthmatic children

Publication	Endpoint	Exposure	Result[1]
Ehrlich et al., 1992	Acute vs non-acute asthma (case-control study)	Any smoker in home	OR 0.84 (0.37-1.89)
		Cigs/day by all smokers	Mean 7.7 vs 10.7 (NS)
		Maternal caregiver smokes	OR 0.64 (0.28-1.44)
		CCR 30+ ng/mg	OR 0.90 (0.39-2.06)
		CCR ng/ml	Mean 46.2 vs 38.5 (NS)
Ogborn et al., 1994	Acute vs when well 3-4 wks later (within child comparison)	Cotinine (ng/ml)	Mean 81 vs 77 (NS)
		CCR (ng/mg)	Mean 93 vs 97 (NS)
		CCR 30+ ng/mg	80% vs 82% (NS)
		Hours exposed in last 48 hrs	Mean 32 vs 32 (NS)
		N cigs smoked at home in last 48 hrs	Mean 31 vs 25 (NS)
		ETS some or a lot	56% vs 44% ($p<0.05$)
Gaspar et al., 2002	Acute vs outpatient asthmatics (case-control study)	Any ETS	OR 6.63 (2.5-17.8)[2]
		Parents smoke	OR 3.51 (2.1-6.0)
		Father smokes	OR 3.0 (1.8-4.9)
		Mother smokes	OR 1.8 (1.0-3.1)
		Other residents at home smoke	OR 1.28 (0.8-2.0)
Karadag et al., 2003	Acute vs when well 4 wks later (within child comparison)	Cotinine (ng/ml)	Mean 295 vs 229.6 (NS)
		CCR (ng/mg)	Mean 314.6 vs 203.8 (NS)
		CCR 30+ ng/mg	81% vs 96% (NS)

[1] Unadjusted for covariates except where stated.

[2] For exposure "Any ETS" only, the OR is adjusted for the variables given in Table 5.4.

Asthma Medication: Table 5.9

Seven studies have related use of asthma medication to ETS exposure. In one study of children hospitalised for asthma (Abulhosn et al., 1997), beta-agonist therapy increased slightly over the 4 weeks following discharge among those living in homes where at least one parent smoked, while among those living in non-smoking homes it substantially reduced. In another study (Schwartz et al., 2000) a within-child analysis estimated that the odds of bronchodilator use were increased 10 fold in association with ETS exposure on the previous day. However, this estimate had very wide confidence limits of 1.3-38.7 and was only marginally significant. Another study (Murray & Morrison, 1988) also reported a marginally significant positive association of recent bronchodilator use with the number of cigarettes smoked by the mother, but not with the number smoked by the father. The other four studies cited in Table 5.9 reported no significant association or indeed any consistent tendency for asthma medication to be increased where ETS exposure was present. The overall data in Table 5.9 do not clearly demonstrate an association of ETS exposure with use of asthma medication.

In one of the studies considered in Table 5.9 (Hu et al., 1997) use of medication was found not to be associated with maternal smoking in pregnancy. Another study (Weitzman et al., 1990b) reported some positive association between current use of asthma medication and maternal smoking in pregnancy. This was not significant for overall smoking, OR 1.75 (0.75-4.07), but was significant for smoking of 10+ cigs/day by the mother, OR 2.66 (1.02-6.91).

Table 5.9. Summary of results for children relating use of asthma medication to ETS exposure

Publication	Endpoint	Exposure	Result[1]
Murray & Morrison, 1988	Recent bronchodilator use	N cigs smoked by mother	Correlation r = 0.12 (p = 0.04)
		N cigs smoked by father	Correlation r = -0.05 (NS)
Abulhosn et al., 1997	Reduction in beta-agonist therapy following hospital discharge (treatments in week 1 and week 4)	Smoking by parents	From 15.3 to 18.0 vs 20.8 to 8.9 (p<0.001)
Hu et al., 1997	Medication in last 2 wks	Mother smoked in last week	OR 0.67 (0.30-1.52)
Dubus et al., 1998	Anti-inflammatory treatment	Detectable cotinine	OR 0.66 (0.19-2.35)
El-Dahr et al., 2000	Bronchodilator use	Parent smoking normally, then reducing	Use said to decrease, but data inconsistent and no statement of significance
Schwartz et al., 2000	Bronchodilator use	ETS on previous day	OR = 10.3 (1.3-38.7)[2]
Halterman et al., 2004	Days using rescue inhaler per 14 days	Smokers in home	Mean 2.51 vs 1.97 (NS)

[1] Unadjusted for covariates except where stated.

[2] Adjusted for child (within-child analysis).

Health Contacts for Asthma: Table 5.10

Three studies have related ETS exposure to frequency of health contacts. Two studies have reported a somewhat higher frequency of contacts in the most ETS exposed children. In one of these (Fergusson & Horwood, 1985) the increase in frequency was only moderate, and the statistical significance was not known, and in the other (Mannino et al., 2002) the excess was larger but not statistically significant. In the third study (Crombie et al., 2001), no significant relationship was seen with cotinine level, but a statistically significant *negative* relationship was seen with three questionnaire-based indices of ETS exposure. The authors of this study, which was restricted to children with at least one smoking parent, suggested that *"this could be due to a lack of awareness of asthma symptoms among heavy smokers or a reluctance to visit the GP."* Factors such as social class or education, which one might expect to be correlated with awareness of asthma symptoms or reluctance to visit the GP, were not adjusted for in this study. It is strange that the multivariate analysis included both cotinine and parental smoking, two correlated markers of ETS exposure. The interpretation of such an analysis is not straightforward. Clearly the overall data do not demonstrate an increase in health contacts in relation to ETS exposure.

No information is available relating health contacts to exposure during gestation.

Table 5.10. Summary of results for children relating health contacts for asthma to ETS exposure

Publication	Endpoint	Exposure	Result[1]
Fergusson & Horwood, 1985	Annual rate of medical consultations for asthma per asthmatic child	Mother smokes cigarettes:	Rate
		None	0.80
		1-10/day	0.53
		11+/day	0.96 (Sig NK)
		Father smokes cigarettes:	Rate
		None	0.82
		1-10/day	0.64
		11+/day	0.85 (Sig NK)
Crombie et al., 2001	Health contacts for asthma (GP, medication, asthma clinic) in last 12 mo	No. of parents who smoke:	IRR[2]
		Father only (base)	1.00
		Mother only	0.76 (0.64-0.89)
		Both parents	0.78 (0.66-0.93)
		Child cotinine level:	IRR
		≤2.0 ng/ml (base)	1.00
		2.1-4.5 ng/ml	0.95 (0.82-1.11)
		>4.5 ng/ml	1.15 (0.98-1.34)
		Amount smoked in home by index parent:	IRR
		0-5 cigs/day (base)	1.00
		6-10 cigs/day	0.81 (0.71-0.92)
		11-15 cigs/day	0.70 (0.59-0.83)
		16-20 cigs/day	0.74 (0.61-0.91)
		>20 cigs/day	0.66 (0.47-0.93)

Table 5.10. (continued)

Publication	Endpoint	Exposure	Result[1]
		Frequency of smoking in room with child:	IRR
		Never (base)	1.00
		Occasionally	0.76 (0.64-0.91)
		Frequently	0.60 (0.48-0.75)
		Every day	0.66 (0.56-0.77)
Mannino et al., 2002	Physician visit in last year for asthma	Highest vs lowest cotinine[3]	OR 1.80 (0.9-3.8)[4]
		Intermediate vs lowest cotinine	OR similar to that for highest vs lowest, and NS

[1] Unadjusted for covariates except where stated.

[2] IRR = incidence rate ratio. Results for number of parents who smoke and child cotinine level are from multivariate analysis which also includes age of child, perceived severity of asthma, severity of asthma by British Thoracic Society (BTS) treatment step and number of children in family. The study was restricted to children where at least one parent smoked.

[3] Serum cotinine groups are 0.050 to 0.115 ng/ml = low, 0.116 to 0.639 ng/ml = intermediate, and 0.640 to 20 ng/ml = high.

[4] Adjusted for age, race/ethnicity, SES, family size and parental history of asthma.

Asthma Severity: Table 5.11

Twelve studies have related ETS exposure to severity of asthma. In one early study (O'Connell & Logan, 1974) significantly increased asthma improvement was seen in children of parents who quit smoking compared to children whose parents continued to smoke. The other 11 studies have related asthma severity to indices of current ETS exposure. Significant positive associations were reported in seven of these studies (Aderele, 1982; Murray & Morrison, 1993; Strachan & Carey, 1995; Callén Blecua et al., 1997; Güler et al., 2000; Al-Ghamdy et al., 2000; Mannino et al., 2002), with non-significant positive associations seen in the remaining four, generally smaller, studies (Wafula et al., 1999; Ratageri et al., 2000; Melén et al., 2001; Wamboldt et al., 2002). However, in those studies that did report significant associations, the associations were not always significant (or even positive) in all analyses. This is most notably evident in the Vancouver study (Murray & Morrison, 1993), where a highly significant ($p<0.001$) positive association between asthma severity and maternal smoking was seen in children studied before July 1986, but a significant ($p<0.05$) *negative* association was seen in children studied later. Also in another study (Aderele, 1982) a significant positive association was seen if the father or older sibling smoked while a non-significant negative association was seen if other household members smoked. Overall, however, the data clearly show a positive association.

Only one study (Güler et al., 2000) related asthma severity to exposure during gestation, finding a significant ($p<0.01$) relationship with the number of cigarettes smoked by the mother.

Table 5.11. Summary of results for children relating asthma severity to ETS exposure

Publication	Endpoint	Exposure	Result[1]
O'Connell & Logan, 1974	Asthma improved (basis not known)	Parent quit smoking	RR 3.38 (1.44-7.91)
Aderele, 1982	Severity of asthma (basis not known):	Household adult smokes regularly	OR
	Mild (base)		1.00 (base)
	Moderate		1.20 (0.67-2.15)
	Severe		1.48 (0.87-2.53)
		Father or older sib smokes regularly	OR
	Mild (base)		1.00 (base)
	Moderate		1.79 (0.87-3.67)
	Severe		2.61 (1.37-4.96)
		Other smoker in household	OR
	Mild (base)		1.00 (base)
	Moderate		0.68 (0.28-1.67)
	Severe		0.50 (0.20-1.29)
Murray & Morrison, 1993	Severity score (based on wheeze, wheeze on exertion, medication)	*Whole study period*	
		Cigs/day by mother	Correlation +0.19 ($p<0.05$)
		Cigs/day by father (in same room)	Correlation –0.04 (NS)
		Before July 1986	
		Mother smokes	Mean 8.2 vs 6.4 ($p<0.001$)
		Father smokes	Mean 7.1 vs 6.7 (NS)
		After July 1986	
		Mother smokes	Mean 5.8 vs 6.6 ($p<0.05$)
		Father smokes	Mean 6.5 vs 6.3 (NS)
Strachan & Carey, 1995	Frequent and speech-limiting attacks vs only one of these	Mother smokes now[2]:	OR
		0 cigs/day (base)	1.00
		1-10 cigs/day	1.69 (0.99-2.88)
		>10 cigs/day	1.86 (0.91-3.77)
		Any	1.74 (1.10-2.76)
		Father smokes now:	OR
		0 cigs/day (base)	1.00
		1-10 cigs/day	1.70 (0.93-3.12)
		>10 cigs/day	1.66 (0.73-3.77)
		Any	1.69 (1.01-2.82)
Callén Blecua et al., 1997	Severe (based on FVC, FEV_1, PEFR and $FEF_{25-75\%}$)	Parents smoke	OR 1.84 (1.12-3.03)
Wafula et al., 1999	Severity (based on frequency of attacks):	Any smoking at home	OR
	Mild (base)		1.00
	Moderate		2.06 (0.96-4.40)
	Severe		Not given

Table 5.11. (Continued)

Publication	Endpoint	Exposure	Result[1]
Al-Ghamdy et al., 2000	Severity (based on Saudi national protocol):	Parents smoke	OR
	Mild (base)		1.00
	Moderate		1.81 (1.08-3.03)
	Severe		2.08 (1.25-3.46)
Güler et al., 2000	Severity score (basis unknown)	N cigs smoked by mother	Correlation $p<0.01$
		N cigs smoked by father	Correlation $p<0.05$
		CCR	NS (data not shown)
Ratageri et al., 2000	Severe (= wheeze most days/nights, restricted activity, growth affected, frequent medication) vs mild	Any family member smokes:	OR[3]
		0 cigs/day (base)	1.00
		1-9 cigs/day	0.66 (0.23-1.90)
		10+cigs/day	2.22 (0.98-5.01)
		Any	1.49 (0.73-3.07)
		Father smokes	1.62 (0.78-3.35)
		Grandfather smokes	1.22 (0.35-4.24)
Melén et al., 2001	Severe (based on inhibited daily activity and steroid use in last year) vs mild/moderate	Smoking at home	OR 3.01 (0.74-12.2)[4]
Mannino et al., 2002	Severity (based on frequency of symptoms/respiratory illnesses in last year):		OR
	Moderate/severe vs mild	Highest vs lowest cotinine[5]	2.7 (1.1-6.8)
	Severe vs moderate/mild		1.9 (0.6-5.7)
		Intermediate vs lowest cotinine	ORs similar to those for highest vs lowest, but NS
Wamboldt et al., 2002	Functional severity score	Smoker in household	Mean 8.00 vs 7.40 (NS)

[1] Unadjusted for covariates except where stated.

[2] Results stated to be similar for mother smoked at time of child's birth.

[3] Unadjusted ORs. OR adjusted for the variables listed in Table 5.4 were not given, but were not significant.

[4] Adjusted for age, heredity, cat, dog, and window condensation.

[5] Serum cotinine groups are 0.050 to 0.115 ng/ml = low, 0.116 to 0.639 ng/ml = intermediate, and 0.640 to 20 ng/ml high.

Asthma Symptoms and Acute Episodes: Table 5.12

Fourteen studies have related asthma symptoms or acute attacks to ETS exposure. In six of the studies (Evans et al., 1987; Dubus et al., 1998; Shamssain & Shamsian, 1999; Ehrlich et al., 2001; Wilson et al., 2001b; Morkjaroenpong et al., 2002) no significant effect was seen and in another (Fergusson & Horwood, 1985) the pattern of results did not seem consistent with an association, though significance could not be estimated. In another study (Seidler et al., 1998) an increase in frequency of attacks associated with smoking by the parents was only marginally significant (p=0.05). The other six studies have reported a significant association for at least some of the relevant endpoints studied. By far the strongest associations seen were the about 10 fold increase in cough and phlegm related to smoking in the home in the last two days in the daily diary study in Finland (Schwartz et al., 2000). Significant associations with ETS exposure were also noted with frequency of acute exacerbations (Chilmonczyk et al., 1993), frequency of symptomatic days, but not symptomatic nights (Abulhosn et al., 1997), days with disturbed sleep and with cough, but not wheeze (El-Dahr et al., 2000), lack of symptom control (Soussan et al., 2003) and frequency of symptomatic days and nights (Halterman et al., 2004). Of the three studies that studied cotinine as a marker, one reported an association, with acute exacerbations (Chilmonczyk et al., 1993) and two did not, with crises (Dubus et al., 1998) and with a symptom score (Ehrlich et al., 2001). While the overall results are certainly heterogeneous they are clearly strongly suggestive of an association.

None of the studies relate asthma symptoms and acute episodes to exposure during gestation.

Table 5.12. Summary of results for children relating asthma symptoms and acute episodes to ETS exposure

Publication	Endpoint	Exposure	Result[1]
Fergusson & Horwood, 1985	Asthmatic attacks (maternal report)	Mother smokes:	Annual rate (per asthmatic)
		0 cigs/day	1.59
		1-10 cigs/day	0.96
		11+ cigs/day	2.03 (Sig NK)
		Father smokes:	
		0 cigs/day	1.55
		1-10 cigs/day	1.60
		11+ cigs/day	1.46 (Sig NK)
Evans et al., 1987	Frequency of days with symptoms	Household member smokes	No significant effect
Chilmonczyk et al., 1993	Acute exacerbations in past 12 months	ETS exposure from household members or at day-care:	Mean
		None	2.2
		Mother or other	2.5
		Mother and other	3.9
		Change per category	+0.83 (+0.39 to +1.26)[2]
		CCR:	
		<10 ng/ml	2.1
		10-39 ng/ml	2.8
		>39 ng/ml	3.6
		Change per category	+0.63 (+0.10 to + 1.07)[2]

Table 5.12. (Continued)

Abulhosn et al., 1997	Symptomatic days (in month following discharge)	Smoking by parents	Mean 3.3 vs 1.4 ($p<0.05$)
	2+ symptomatic days		RR 4.00 (1.08-14.75)
	Symptomatic nights		Mean 2.3 vs 1.4 (NS)
Seidler et al., 1998	Increase in frequency of asthma attacks during follow-up	Smoking by parents	OR 1.7 (1.0-3.0)[2]
Dubus et al., 1998	Crises per year	Detectable cotinine	Mean 4.1 vs 4.4 (NS)
	Symptoms between crises		OR 0.49 (0.15-1.60)
Shamssain & Shamsian, 1999	Speech limitation during wheezing attack in past 12 months	Parents smoking:	
		Neither	13.1%
		One parent	14.0%
		Both parents	15.0% (NS)
El-Dahr et al., 2000	Symptom score	Parents smoking normally, then reducing	Mean 1.00 vs 0.54 ($p<0.05$)
	Days with disturbed sleep		15% vs 9% ($p<0.01$)
	Days with cough		30% vs 13% ($p<0.01$)
	Days with wheeze		22% vs 15% (NS)
Schwartz et al., 2000	Cough	Smoking in the home in last 2 days	OR 12.4 (2.4-63.3)
	Phlegm production		OR 7.8 (1.4-41.7)
Ehrlich et al., 2001	Symptom score 8-10 vs 4-7	CCR (ng/mg)	GMean 64.1 vs 72.8 (NS)
Wilson et al., 2001b	Symptom-free days per 2 wk	Intervention effect	Mean diff -0.22 (NS)[3]
	Nights awakened per 2 wk		Mean diff -0.37 (NS)[3]
Morkjaroenpong et al., 2002	Nocturnal symptoms at least 2 nights per month	ETS exposure from caregiver:	OR[4]
		0 cigs/day (base)	1.00
		1-9 cigs/day	0.51 (0.30-0.85)
		10+ cigs/day	1.31 (0.68-2.50)
		Any	0.75 (0.49-1.15)
Soussan et al., 2003	Symptom control[5]	Smoker in home	OR 0.34 (0.13-0.91)[6]
		Mother smokes in home	OR 0.53 (0.20-1.37)
Halterman et al., 2004	Symptom-free days per 2 wk	Smokers in home	Mean 9.69 vs 10.97 ($p<0.01$)
	Symptom days per 2 wk		Mean 3.07 vs 2.07 ($p<0.01$)
	Symptom nights per 2 wk		Mean 3.05 vs 2.05 ($p<0.01$)

[1] Unadjusted for covariates except where stated.

[2] Adjusted for the variables given in Table 5.4.

[3] Intervention vs control, with adjustment for baseline differences.

[4] ORs are unadjusted. The authors also report an OR, adjusted for the variables given in Table 5.4, of 2.83 (1.22-6.55) for 10+ vs 1-9 cigs/day. This illogical analysis has not been included in the main body of the table.

[5] Symptom control is defined as diurnal and nocturnal asthma <1/wk and no symptoms between attacks at all visits in 2nd and 3rd years of follow up.

[6] OR for smoker in the home is adjusted for the variables given in Table 5.4, but OR for mother smokes in the home is unadjusted.

Quality of Life and General Health: Table 5.13

Two studies have related ETS exposure to AQOL. In one study (Wamboldt et al., 2002) children with a smoker in the household had a non-significantly lower AQOL as assessed by the child but a significantly lower AQOL as assessed by the parent. In the other study (Halterman et al., 2004) no association was seen between ETS exposure and change in AQOL (in the intervention and usual care groups combined). Table 5.13 also includes results from one study (Mannino et al., 2002) showing no significant relationship of cotinine level to general health. This endpoint is clearly not very directly related to asthma specifically. These data are too limited for any useful conclusions to be drawn.

Table 5.13. Summary of results for children relating quality of life and general health to ETS exposure

Publication	Endpoint	Exposure	Result[1]
Mannino et al., 2002	Less than very good health	Highest vs lowest cotinine[2]	OR 1.3 (0.7-2.5)
		Intermediate vs lowest cotinine	OR similar to that for highest vs lowest, and NS
Wamboldt et al., 2002	Parent-assessed AQOL[3]	Smoker in household	Mean 5.38 vs 6.13 ($p<0.01$)
	Child-assessed AQOL		Mean 5.61 vs 5.77 (NS)
Halterman et al., 2004	Change in AQOL[3] during study year	Smokers in home	Mean 0.55 vs 0.36 (NS)

[1] Unadjusted for covariates except where stated.

[2] Serum cotinine groups are 0.050 to 0.115 ng/ml = low, 0.116 to 0.639 ng/ml = intermediate, and 0.640 to 20 ng/ml = high.

[3] AQOL = Asthma-related qualify of life. Lower scores indicate poorer quality.

Summary of Results Presented in Tables 5.5 to 5.13

The data presented in Tables 5.5 to 5.13 relate to a wide variety of endpoints and indices of exposure, with results presented in various ways. Formal meta-analysis of the combined data is not practical. However Table 5.14 summarizes the results for each study in Tables 5.5 to 5.13 on a symmetrical 7 point scale as follows:

1. Decrease in risk – significant at $p<0.05$
2. Decrease in risk – not significant – by more than a factor of 1.5
3. Decrease in risk – not significant – by at most a factor of 1.5
4. No effect (association stated to be not significant but data not shown)
5. Increase in risk – not significant – by at most a factor of 1.5
6. Increase in risk – not significant – by more than a factor of 1.5
7. Increase in risk – significant at $p<0.05$

Here an "increase" not only includes cases where an increase in an adverse health effect (or a decrease in a beneficial health effect) was associated with ETS exposure, but where a reduction in risk of an adverse health effect was associated with intervention to reduce ETS exposure (El-Dahr et al., 2000; Wilson et al., 2001b). For each study in each table, only one

result is counted. Where there is a choice of ETS exposure indices preference is given to those based on mean cotinine, mean CCR, total ETS exposure and smoking by the mother in that order. Results are normally included in Table 5.14 based on the exposed/unexposed result, but the highest exposure level is used if only dose-response data are available.

It is evident that the overall data in Table 5.14 are consistent with a positive association. Of the 64 results summarised, 27 show a significant positive association and only two (Murray & Morrison, 1993 for asthma severity for results after July 1986 and Mannino et al., 2002 for hospitalisation) a significant negative one. Similarly, there are seven non-significant increases by a factor of 1.5 or more as compared to two non-significant decreases by the same factor. While the data are heterogeneous, with many studies showing little effect if any and a few very strong relationships, it is clear the overall pattern of results is not due to chance. This conclusion would have been unaffected by alternative plausible rules for preferring which results to include from studies providing a choice of ETS exposure variables.

Table 5.14. Summary of associations presented in Tables 5.5 to 5.13

			Decreased risk			No effect	Increased risk		
			Significant	Not significant			Not significant		Significant
Table	Endpoint	No of studies	at p<0.05	by >1.5	by ≤1.5		by ≤1.5	by >1.5	at p<0.05
5.5	Hospitalisation	9	1	1	0	1	1	1	4
5.6	ER visits and urgent consultations	6	0	0	1	0	1	0	4
5.7	Restricted activity	6	0	0	1[1]	0	1	2	2
5.8	Acute and non-acute asthma	4	0	0	0	0	3	0	1
5.9	Asthma medication	7	0	1	1	0	2[2]	0	3
5.10	Health contacts for asthma	3	0	0	0	0	2[3]	1	0
5.11	Asthma severity	13[4]	1	0	1	0	3	2	6[5]
5.12	Asthma symptoms and acute episodes	14	0	0	4[6]	1	1	1[3]	7[7]
5.13	AQOL and general health	3	0	0	1	0	1	0	1[8]
	TOTAL	64[9]	2	2	9	2	15	7	27[9]

ER = emergency room or department, AQOL = asthma-related quality of life

[1] Choosing data for limited physical activity from Morkjaroenpong et al. (2002).

[2] Including result for El-Dahr et al. (2000).

[3] Including results from Fergusson & Horwood (1985).

[4] Counting as two separate studies results before and after July 1986 from Murray & Morrison (1993).

[5] Including result for moderate/severe vs mild from Mannino et al. (2002).

[6] Choosing data for crises per year from Dubus et al. (1998) and from Wilson et al. (2001b).

[7] Choosing data for symptomatic days from Abulhosn et al. (1997) and for symptom score from El-Dahr et al. (2000).

[8] Choosing data for parent-assessed AQOL for Wamboldt et al. (2002).

[9] Only counting once the significant increase reported for Dales et al., 2002 in Tables 5.5 and 5.6

5.2.2. Lung Function

Table 5.15 summarizes results from 18 studies relating ETS exposure to five lung function variables: FEV_1, FVC, the ratio of FEV_1 to FVC, $FEF_{25-75\%}$ and PEFR.

FEV_1

Seven of the 12 studies providing data for FEV_1 reported no significant association with ETS exposure (Evans et al., 1987; O'Connor et al., 1987; Chilmonczyk et al., 1993; Callén Blecua et al., 1997; Dubus et al., 1998; Venners et al., 2001; Wilson et al., 2001b). In the Vancouver study (Murray & Morrison, 1993) no significant association of FEV_1 with parental smoking was seen for children studied after July 1986. However, for children born before July 1986, FEV_1 was significantly reduced if either the mother or the father smoked. In the Southern California study (Li et al., 2000), current smoking was not associated with FEV_1 but past ETS exposure was associated with a significantly ($p<0.05$) reduced FEV_1 in boys but not girls. In the Cape Town study (Ehrlich et al., 2001), current smoking by the mother was associated with a significantly ($p<0.05$) reduced FEV_1, but no significant association was seen with other indices of parental smoking or with cotinine. In the analyses based on NHANES III, no significant association was seen between FEV_1 and smoking at the home (Chapman et al., 2003) but FEV_1 was significantly lower in those with high cotinine (0.640+ ng/ml) than in those with low cotinine (<0.116 ng/ml) (Mannino et al., 2002). The most significant association seen ($p<0.001$) was in the New Orleans study (El-Dahr et al., 2000) where FEV_1 was found to improve in 15 out of 17 children when the parents reduced the amount they smoked. As noted previously, this study lacked a proper control group. Overall these data do not provide very clear evidence that ETS exposure is associated with reduced FEV_1.

FVC

Four of the studies with relevant data reported no significant association of FVC with ETS exposure (O'Connor et al., 1987; Callén Blecua et al., 1997; Dubus et al., 1998; Venners et al., 2001). In the Vancouver study (Murray & Morrison, 1989) no relationship was seen with maternal smoking, but a marginally significant ($p=0.05$) reduced FVC was seen where the father smoked. In the study in Southern California (Li et al., 2000) no association of FVC with ETS exposure was seen in boys, but in girls, children with 2 or more current smokers in the household had a significantly ($p<0.05$) *increased* FVC. As for FEV_1, the results from NHANES III showed no association of FVC with the number of smokers in the home (Chapman et al., 2003) but did show a significantly ($p<0.05$) reduced FVC in the high cotinine group (Mannino et al., 2002). The combined data for FVC do not clearly demonstrate the existence of an association.

FEV_1/FVC

No significant association was reported in most studies (Callén Blecua et al., 1997; Venners et al., 2001; Mannino et al., 2002; Chapman et al., 2003). In the Southern California study (Li et al., 2000) a significantly ($p<0.05$) reduced FEV_1/FVC was seen in relation to past ETS exposure in boys, but no association was seen in relation to current smoking or in girls. The study in Portland (Chilmonczyk et al., 1993) reported a significant ($p<0.05$) reduction in

FEV_1/FVC associated with household or day care smoking and cotinine. More data are needed to reach any clear conclusion here.

$FEF_{25-75\%}$

Of the eight studies providing evidence, three (Evans et al., 1987; O'Connor et al., 1987; Dubus et al., 1998) did not find a significant association of $FEF_{25-75\%}$ with ETS exposure. The remaining five did report a significant association, but often only in some analyses. Thus the Vancouver study (Murray & Morrison, 1993) reported a highly significant ($p<0.001$) reduction if the mother smoked for children born before July 1986, but a non-significant increase for children born after July 1986, and no association with father smoking in either period. Also, while the study in Southern California (Li et al., 2000) reported a significant ($p<0.05$) reduction in boys but not girls (and then only in relation to past but not current ETS exposure), the NHANES III study (Chapman et al., 2003) reported a significant ($p<0.05$) reduction in girls but not boys associated with having two smokers in the home. Significant ($p<0.05$) reductions were also reported in NHANES III (Mannino et al., 2002) in relation to cotinine level, and in the Portland study (Chilmonczyk et al., 1993) in relation to household or day care smoking and cotinine. The significant results for $FEF_{25-75\%}$ from the Istanbul study (Güler et al., 2000) are for increased reversibility and are not directly comparable to the other data. Overall, the data for $FEF_{25-75\%}$ are more suggestive of an association with ETS than is the case for FEV_1, FVC or FEV_1, but there are still inconsistencies which need resolution.

PEFR

The data included in Table 5.15, from 10 studies, are for a variety of endpoints, including PEFR variability (Frischer et al., 1993), PEFR amplitude (Meijer et al., 1996), PEFR reversibility (Güler et al., 2000) and PEF control (Soussan et al., 2003) as well as PEFR level (Evans et al., 1987; Chan & Chen, 1995; Callén Blecua et al., 1997; Dubus et al., 1998; Schwartz et al., 2000; El-Dahr et al., 2000). Of the five studies where significant associations were noted, three (Chan & Chen, 1995; El-Dahr et al., 2000; Güler et al., 2000) were only incompletely reported in abstracts, one (Frischer et al., 1993) reported an association only in non-atopic children and one (Chan & Chen, 1995) reported an association with cotinine only for samples collected at night and not during the day. The study in Finland (Schwartz et al., 2000) reported a significantly ($p<0.05$) reduced PEFR associated with ETS exposure in between-child comparisons, but not in within-child comparisons. Taken as a whole, these data are difficult to interpret.

Other Lung Function Variables

There are very limited data for other lung function variables that are not shown in Table 5.15. In the study in Marseilles (Dubus et al., 1998; Oddoze et al., 1999) no association was found between cotinine level and SRAW. In NHANES III (Chapman et al., 2003) $FEF_{25-75\%}$/FVC was not associated with smoking in the household in boys (levels 0.791, 0.771, 0.796 for 0, 1, 2+ smokers in the home) but was significantly ($p<0.05$) lower in more heavily exposed girls (levels 1.265, 1.243, 1.054).

Table 5.15. Summary of results for children relating lung function to ETS exposure

Publication	Exposure	Lung function variable				
		FEV_1	FVC	FEV_1/FVC	$FEF_{25-75\%}$[1]	PEFR
Evans et al., 1987	No household smoker	1.49ℓ			1.42ℓ/sec	2.74ℓ/sec
	Household smoker	1.60ℓ			1.60ℓ/sec	3.19ℓ/sec
	p	NS			NS	NS
O'Connor et al., 1987	Mother non-smoker	102.9%	104.0%		85.8%	
	Mother smoker	100.8%	107.8%		76.1%	
	p	NS	NS		NS	
Frischer et al., 1993	Effects of mother smoking in non-atopic children					+54.7%[2], p<0.05
	Effect of mother smoking in atopic children					-8.5%[2], NS
Chilmonczyk et al., 1993	No household or day-care smoker	109.3%		83.7%	85.4%	
	Mother or others smoke	102.4%		79.4%	71.8%	
	Mother and others smoke	102.2%		80.0%	73.6%	
	Trend p	NS		p<0.05	p<0.05	
	Cotinine <10 ng/ml	108.8%		83.5%	85.4%	
	10-39 ng/ml	105.2%		81.2%	74.9%	
	40+ ng/ml	98.5%		77.5%	67.3%	
	Trend p	NS		p<0.05	p<0.05	
Murray & Morrison, 1993	*Before July 1986:*					
(FVC data are from	Mother non-smoker	84.4%	93.8%		71.7%	
Murray & Morrison, 1989)	Mother smoker	77.3%	91.2%		59.5%	
	p	p<0.01	NS		p<0.001	
	Father non-smoker	84.2%	94.5%		70.0%	
	Father smoker	80.2%	90.6%		67.1%	
	p	p<0.05	p=0.05		NS	

Table 5.15. (continued)

Publication	Exposure	Lung function variable				
		FEV_1	FVC	FEV_1/FVC	$FEF_{25-75\%}$[1]	PEFR
	After July 1986:					
	Mother non-smoker	90.8%			79.4%	
	Mother smoker	91.3%			81.0%	
	p	NS			NS	
	Father non-smoker	90.1%			78.0%	
	Father smoker	93.0%			84.1%	
	p	NS			NS	
Chan & Chen, 1995	Cotinine/creatinine ratio (CCR)					CCR significantly higher where PEFR<80% of predicted for samples collected at night, not during the day
Meijer et al., 1996	*During ICS*[3]*:*					
	Parents non-smokers					20.6%
	Parent smokes					28.7%
	p					NS
	After ICS withdrawal[3]*:*					
	Parents non-smokers					19.4%
	Parent smokes					29.7%
	p					p<0.05
Callén Blecua et al., 1997	Parents non-smokers	93.7%	97.4%	76.7%		92.6%
	Parent smokes	91.9%	96.9%	72.7%		87.2%
	p	NS	NS	NS		NS
Dubus et al., 1998	No cotinine	101.9%	101.7%		104.3%	85.6%
	Detectable cotinine	106.5%	106.6%		94.0%	89.1%
	p	NS	NS		NS	NS

Table 5.15. (continued)

Publication	Exposure		Lung finction variable				
			FEV_1	FVC	FEV_1/FVC	$FEF_{25-75\%}$	PEFR
El-Dahr et al., 2000	Parent smoking normally then reducing		Improved in 15/17				Improved in 8/15, worsened in 1/15
	p		<0.001				p<0.05
Güler et al., 2000[4]	Mother smokes now					Higher	?
	p					p=0.03	NS?
	Mother smoked in pregnancy					Higher	Higher
	p					p=0.001	Significant(NOS)
Li et al., 2000[5]	*Boys:*	Past ETS	-4.9, p<0.05	-2.2, NS	-2.8, p<0.05	-9.2, p<0.05	
		One current smoker	-3.9, NS	-3.3, NS	-0.6, NS	-4.0, NS	
		Two+ current smokers	-2.9, NS	+0.8, NS	-3.6, NS	-5.2, NS	
	Girls:	Past ETS	+2.1, NS	+2.5, NS	-0.2, NS	+1.4, NS	
		One current smoker	+1.1, NS	+1.9, NS	-0.8, NS	+7.0, NS	
		Two+ current smokers	+2.7, NS	+5.9, NS	-2.7, NS	-4.2, NS	
Schwartz et al., 2000[6]	Any ETS at home a.m.						-41.9 ℓ/min, p<0.05
	Any ETS at home p.m.						-40.7 ℓ/min, p<0.05
	ETS previous day						-9.2 ℓ/min, NS
Ehrlich et al., 2001	Mother not current smoker		1.64ℓ				
	Mother current smoker		1.41ℓ				
	p		p<0.05				
	Mother never smoked		1.47ℓ				
	Mother ever smoked		1.53ℓ				
	p		NS				
	Mother did not smoke in child's 1st yr		1.56ℓ				
	Mother smoked in child's 1st yr		1.46ℓ				
	p		NS				
	Father not current smoker		1.45ℓ				
	Father current smoker		1.56ℓ				

Table 5.15. (continued)

Publication	Exposure		Lung finction variable				
			FEV_1	FVC	FEV_1/FVC	$FEF_{25-75\%}$	PEFR
	p		NS				
	Father did not smoke in child's 1st yr		1.50ℓ				
	Father smoked in child's 1st yr		1.52ℓ				
	p		NS				
	Not 2+ smokers in household		1.59ℓ				
	2+ smokers in household		1.46ℓ				
	p		NS				
	CCR	1st quartile	1.47ℓ				
		2nd quartile	1.47ℓ				
		3rd quartile	1.65ℓ				
		4th quartile	1.42ℓ				
		Trend p	NS				
Venners et al., 2001[7]	*Boys:*	Father current <30 cigs/day	-1.9%, NS	-1.8%, NS	"No important		
		30+ cigs/day	-3.7%, NS	-3.7%, NS	association"		
	Girls:	Father current <30 cigs/day	-1.0%, NS	-0.4%, NS	"No important		
		30+ cigs/day	-1.3%, NS	-0.8%, NS	association"		
Wilson et al., 2001b[8]	Intervention effect		-0.41%				
	p		NS				
Mannino et al., 2002[9]	Difference high vs low cotinine		-8.1%	-5.6%	-3.0%	-12.5%	
	p		p<0.05	p<0.05	NS	p<0.05	
	Difference intermediate vs low cotinine		Not given	Not given	Not given	Not given	
	p		NS	NS	NS	NS	

Table 5.15. (continued)

Publication	Exposure		Lung finction variable				
			FEV_1	FVC	FEV_1/FVC	$FEF_{25-75\%}$	PEFR
Chapman et al., 2003[10]	*Boys:*	No smoking at home (base)	2.61ℓ	3.16ℓ	82.6%	2.50 ℓ/s	
		1 smoker at home	2.65ℓ	3.21ℓ	82.5%	2.65 ℓ/s	
		p	NS	NS	NS	NS	
		2 smokers at home	2.39ℓ	2.93ℓ	81.5%	2.33 ℓ/s	
		p	NS	NS	NS	NS	
	Girls:	No smoking at home (base)	2.92ℓ	3.13ℓ	93.1%	3.96 ℓ/s	
		1 smoker at home	3.02ℓ	3.24ℓ	93.2%	4.03 ℓ/s	
		p	NS	NS	NS	NS	
		2 smokers at home	2.72ℓ	3.06ℓ	88.9%	3.22 ℓ/s	
		p	NS	NS	NS	$p<0.05$	
Soussan et al., 2003[11]	Smoker in home						OR 0.73 (0.39-1.38)
	Mother smokes at home						OR 0.34 (0.14-0.89)

[1] Including MMEFR.

[2] Data are percentage increase in PEFR variability in children with a smoking mother.

[3] ICS = inhaled corticosteroids. PEFR values are PEFR amplitude = (maximum-minimum)/mean based on 24 hour data.

[4] Data are for FEF and PEF reversibility. Significance not stated for PEF reversibility and smoking now but presumably not significant.

[5] Data are percentage differences vs no ETS exposure and are irrespective of *in utero* exposure.

[6] Data are average changes over a 3 month period. For any ETS exposure at home they derive from a between-child analysis, while for ETS previous day they derive from a within-child analysis.

[7] Data are changes relative to father never smoker.

[8] "Intervention effect" is change in intervention group from baseline to follow-up relative to corresponding change in usual care group.

[9] Cotinine groups are 0.050 to 0.115 ng/ml = low, 0.116 to 0.639 ng/ml = intermediate, 0.640 to 20 ng/ml = high.

[10] Values are model-predicted (see Chapman et al., 2003 Table 5.4).

[11] Data are for PEF control (<20% variability) vs lack of control.

Overall Conclusions for Lung Function

While there are a number of statistically significant findings in Table 5.15, the data generally do not show a very consistent pattern. Often associations are seen only for subsets of the data (Murray & Morrison, 1993; Chan & Chen, 1995; Meijer et al., 1996; Li et al., 2000; Chapman et al., 2003) or for some indices of exposure and not others (Murray & Morrison, 1993; Schwartz et al., 2000; Li et al., 2000; Ehrlich et al., 2001), with some studies reporting no significant associations at all (Evans et al., 1987; O'Connor et al., 1987; Callén Blecua et al., 1997; Dubus et al., 1998; Venners et al., 2001; Wilson et al., 2001b; Soussan et al., 2003). A clear relationship of ETS exposure to reduced lung function has not been established, though the data are somewhat suggestive of a relationship, particularly for $FEF_{25-75\%}$.

5.2.3. Bronchial Responsiveness

Seven studies have related ETS exposure to bronchial responsiveness.

In the Boston study (O'Connor et al., 1987) the response to cold air challenge (fall in FEV_1 as a percentage of predicted FEV_1) was greater if the mother smoked (24% vs 11.9% for mother non-smoker), but not if the father smoked (15% vs 17.1% for father non-smoker). The association with maternal smoking was significant ($p=0.02$) using one statistical technique, but not ($p=0.07$) using another.

In the Viterbo study (Martinez et al., 1988) the response to carbachol (fall of >20% FEV_1) was significantly ($p<0.05$) greater if the parents smoked, the OR being estimated as 18.7, but with a very wide confidence interval of 1.5 to 232.3.

In the Vancouver study bronchial responsiveness to histamine was reported to be significantly related to maternal but not paternal smoking in the first few papers describing results (Murray & Morrison, 1986; Murray & Morrison, 1988; Murray & Morrison, 1989; Murray & Morrison, 1992). In the final paper (Murray & Morrison, 1993) the increase in bronchial responsiveness (reduction in lung PC_{20}) in relation to maternal smoking was evident only in children examined before July 1986 (mother smoker –0.23, mother non-smoker +0.44, $p<0.05$) but not in children examined afterwards (+0.41 vs +0.26, NS). The same tendency was evident for father smoking (+0.12 vs +0.32, NS before July 1986; +0.74 vs +0.10, NS after July 1986).

In the Freiburg study (Frischer et al., 1992; Meinert et al., 1994) bronchial responsiveness to an exercise test (15% decrease in PEFR) was higher if the mother had smoked before pregnancy (OR 1.7) or had smoked when the child was 1 year old (OR 2.2), but was lower if the mother smoked when the test was done at age 8 (OR 0.5). These differences were non-significant in univariate analyses. Multivariate analyses implausibly claimed a significant 20 fold increase in bronchial responsiveness associated with maternal smoking at age 1 and a significant 20 fold decrease associated with maternal smoking at age 8. However these analyses are highly open to question because of the inter-correlations of the maternal smoking variables.

In the Marseilles study (Dubus et al., 1998) the response to carbachol (concentration to produce a 2-fold increase in SRAW) was significantly ($p<0.05$) decreased in children with a detectable cotinine (108.3 vs 160.9 for undetectable) but was non-significantly decreased if the mother smoked (98.4 vs 147.2 for father smoked or parents did not smoke). The

percentage of bronchodilation was significantly ($p<0.05$) increased in children with a detectable cotinine (74.8 vs 68.8), but was not significantly related to parental smoking (data not given).

In the New Orleans study (El-Dahr et al., 2000) the response to methacholine challenge did not vary between the 3 month period where smokers in the child's household smoked normally and the 3 month period where they were encouraged to quit. 7 of 17 children improved, and 7 worsened, with the other 3 showing no change.

In the Cape Town study (Ehrlich et al., 2001) bronchial responsiveness to histamine (fall of >20% FEV_1) was found not to be significantly related to cotinine (OR 1.00, 0.86, 0.94, 0.81 for 4 quartiles) or a variety of indices of parental smoking (e.g. mother current smoker OR 0.78, CI 0.54-1.12 or father current smoker OR 0.99, CI 0.78-1.27).

Taken as a whole these data do not show a consistent relationship of ETS exposure to bronchial responsiveness.

5.3. SUMMARY AND CONCLUSIONS

5.3.1. Summary

Sixty relevant publications, apparently relating to 47 separate studies, were identified. 34 of the studies were first reported in the last 10 years (1995 to 2004). Results were available from a total of 22 countries, with more studies (18) conducted in the USA than in other countries. The median number of asthmatics studied was 167 per study, the largest study involving 3010. Studies generally were of both sexes, with more boys than girls. Most studies covered an age range of a few years, with 6-9 year olds most commonly studied. A few studies specifically excluded smokers.

There were a variety of study designs, including one experimental and three intervention studies, but most studies were of cases identified through medical records, or cross-sectional studies with the classification of asthma based on questionnaire. Eight of the 47 studies used a nicotine-based marker of ETS exposure, with other studies relying on questionnaire response. Only eight studies recorded maternal smoking in pregnancy.

About half the studies did not adjust for any potential confounding variables, with some potential confounding variables (such as diet, exercise and recent respiratory infections) rarely adjusted for.

A wide variety of indices of asthma exacerbation and severity were used in the studies, and the results are summarized under nine different endpoints. The endpoints, the number of studies providing data, the number showing a significant positive (negative) association with ETS exposure are summarized in the table on the next page.

Overall, these data show considerable evidence of an association, though the results appear heterogeneous, with a few studies reporting very strong relationships and a number no positive relationship at all. However, interpretation of this association is not straightforward for a number of reasons. These include the lack of clear evidence that increases in ETS exposure within child are associated with exacerbations of asthma, limited reporting of relevant study details by many authors (including information on active smoking by the child) and failure to separate out results by sex and by age. Failure to control for potential

confounding variables is also a feature of the studies. No studies adjusted for maternal smoking in pregnancy, only six for any social class related variables, only four for infections in the child (and none for infections in the parent) and few even take the sex or age of the child into account. Furthermore, some of the various endpoints used may not be very direct or reliable measures of asthma severity.

Endpoint	Number of studies	Number significant +ve (-ve)	Conclusion/comment
Hospitalisation	9	4 (1)	Some evidence of an association, but data from NHANES III conflict
ER visits and urgent consultations	6	4 (0)	Evidence of an association
Restricted activity	6	2 (0)	Association not demonstrated
Acute and non-acute asthma	4	1 (0)	No clear difference in ETS exposure between acutely and non-acutely asthmatic children
Asthma medication	7	3 (0)	Association not clearly demonstrated.
Health contacts for asthma	3	0 (0)	No association shown
Asthma severity	13	6 (1)	Clear positive association
Asthma symptoms and acute episodes	14	7 (0)	Results heterogenous, but strongly suggestive of an association
AQOL and general health	3	1 (0)	Data too limited to draw conclusions
Total	64[1]	27[1] (2)	Overall data clearly show a positive association, not attributable to chance

ER = emergency room or department, AQOL = asthma-related quality of life.

[1] For one study, the same significant result has been reported under both the first two endpoints, but is only counted once in the totals.

Very few studies investigated these endpoints in relation to maternal smoking in pregnancy. There were five reported results, of which two (for asthma medication and severity) showed a significant positive association.

Eighteen studies related ETS exposure to one or more of five lung function variables – FEV_1, FVC, the ratio of FEV_1 to FVC, $FEF_{25-75\%}$ and PEFR. The data for $FEF_{25-75\%}$ are more suggestive of an association with ETS than is the case for FEV_1, FVC or the FEV_1/FVC ratio, but there are still inconsistencies which need resolution. The data on PEFR relate to a variety of endpoints, and the results, which are incompletely reported, are difficult to interpret. Other lung function variables have only very rarely been studied. While a number of statistically significant findings have been reported for lung function, the data generally do not show a very consistent pattern, with associations seen only for subsets of the data or for some indices of exposure and not others, with some studies reporting no significant associations at all. A clear relationship of ETS exposure to reduced lung function has not been established, though the data are somewhat suggestive of a relationship.

Seven studies have related ETS exposure to bronchial responsiveness, but no consistent association has been shown.

5.3.2. Other Reviews of the Evidence

An early review published by the Canadian Paediatric Society (Canadian Paediatric Society, 1986) was entitled *"Secondhand cigarette smoke worsens symptoms in children with asthma."* Although its conclusions were consistent with its title, only two of the 25 references cited actually concerned exacerbation of asthma. One was an experimental chamber study considered in Chapter 3 (Dahms et al., 1981), the other the study in Vancouver (Murray & Morrison, 1986) which reported that severity of asthma was increased if the mother smoked, but not if the father did. Most of the evidence cited related to healthy children, not asthmatics, so the conclusion that *"There is little doubt that cigarette smoke worsens asthma"* seems invalid, based on the evidence presented.

Ehrlich et al. (1993) published a review entitled *"Is passive smoking a cause of asthma in children?"* Although the authors noted the distinction between studies of asthma induction and studies of asthma exacerbation, the studies cited to support the conclusion that there is *"consistent evidence that among children already asthmatic, maternal smoking is associated with more severe asthma, more frequent visits to the emergency room, and greater bronchial hyperresponsiveness"* included a number not relevant to exacerbation. The only relevant studies cited were the series of studies in Vancouver (Murray & Morrison, 1986; Murray & Morrison, 1988; Murray & Morrison, 1989) and two others (Evans et al., 1987; Frischer et al., 1992). Although the review was rather short for such a complex issue, it did refer to a number of important possibilities of confounding that need to be controlled for, including socio-economic status, active smoking and symptom prevalence in parents.

For each of a number of studies on ETS and asthma published by 1992, the US EPA report *"Respiratory health effects of passive smoking: lung cancer and other disorders"* (National Cancer Institute, 1993) presented a paragraph summarizing the results. These included only four studies relevant to asthma exacerbation (Evans et al., 1987; O'Connor et al., 1987; Murray & Morrison, 1989; Ehrlich et al., 1992). The EPA report concluded: *"There is now sufficient evidence to conclude that passive smoking is causally associated with additional episodes and increased severity of asthma in children who already have the disease. Several studies have found that bronchial responsiveness is more prevalent and more intense among asthmatic children exposed to maternal smoke. Emergency room visits are more frequent in children of smoking mothers, and these children also have been found to need more medication for their asthma than do children of nonsmoking mothers."* Since one of the studies cited showed no significant relationships with ETS exposure (Ehrlich et al., 1992), one was extremely small (O'Connor et al., 1987), and one reported a significant relationship with only one of a range of endpoints studied (Evans et al., 1987), these conclusions seem unjustified based on this limited evidence.

A short review of *"passive smoking in childhood"* (Di Benedetto, 1995) included a section on *"asthma and bronchial responsiveness."* The author stated that *"it is well known that maternal cigarette smoking aggravates asthma symptoms and bronchial responsiveness in children with an established diagnosis of the disease,"* citing associations with increased use of health services, asthma medications and asthma symptoms. No references were cited and the review was very far from comprehensive. The author noted that *"the mechanisms by which passive smoking might increase bronchial responsiveness is still unclear"* and it is possible that *"children exposed to passive smoking might exhibit an increased risk of acquiring severe viral infections, which might cause bronchial hyperresponsiveness."*

The California EPA report *"Health effects of exposure to environmental tobacco smoke"* (National Cancer Institute, 1999) reviewed epidemiologic evidence on asthma exacerbation in children, reaching the conclusion that

> "The studies reviewed … support the previous finding by the U.S. EPA (1992) that there is 'sufficient evidence … that passive smoking is causally associated with additional episodes and increased severity of asthma in children who already have the disease.'"

The main body of the section consisted of mini-reviews of studies identified by them as relevant. They failed to mention some early studies we cite (including O'Connell & Logan, 1974; Gortmaker et al., 1982; Aderele, 1982; Fergusson & Horwood, 1985; Martinez et al., 1988; Weitzman et al., 1990a; Weitzman et al., 1990b; Frischer et al., 1992; Frischer et al., 1993) as well as any study published between 1995 and 1997, with one exception (Strachan & Carey, 1995), so missing eight studies we consider (Chan & Chen, 1995; LeSon & Gershwin, 1995; Jindal et al., 1996; MacArthur et al., 1996; Meijer et al., 1996; Abulhosn et al., 1997; Hu et al., 1997; Callén Blecua et al., 1997). While the report generally summarized the results of the studies accurately enough, they were uncritical as they failed to detect obvious flaws we have noted in section 5.1. These include the failure to properly investigate interactions with age and sex in the third Vancouver paper (Murray & Morrison, 1989) and to detect the lack of association with ETS exposure in the second half of the Vancouver study (Murray & Morrison, 1993).

The review also had some strange statements. These included the unsound view that the Denver study (Ostro et al., 1994) which *"had more than 10,000 observations, … afforded substantial power to detect associations with indoor exposures, including ETS."* But power depends mainly on the number of subjects, and only 164 asthmatics were studied! Also, having described the Sheffield study (Strachan & Carey, 1995) they concluded that *"This study examines risk factors for having severe asthma versus not having asthma at all; it does not address whether exposure to ETS or other factors influence the severity of asthma among children who already have the disease."* If so, why include it in the section? In fact, one can extract relevant data (see section 5.1.4), but these are not the data they cited. Where associations were not seen, comments were often made about lack of power and of possible underestimation of effects due to misclassification of exposure. The section contained no discussion whatsoever of any potential sources of possible bias. Nor did it contain any linking paragraphs between the mini-reviews and the conclusion to describe how the conclusion was reached. As such, the section was totally one-sided and unscientific, and provided no valid support for its conclusions.

Of a series of papers on effects of parental smoking on the respiratory health of children published in Thorax by the group from St George's Hospital Medical School, two dealt specifically with data on asthma exacerbation.

The first, entitled *"Parental smoking and childhood asthma: longitudinal and case-control studies"* (Strachan & Cook, 1998a), reviewed epidemiological studies in healthy children as well as in asthmatics. It concluded that:

> "The excess incidence of wheezing in smoking households appears to be largely non-atopic 'wheezy bronchitis' with a relatively benign prognosis, but among children with established asthma, parental smoking is associated with more severe disease. This apparent paradox may

be reconciled if environmental tobacco smoke is considered a co-factor provoking wheezing attacks, rather than a cause of the underlying asthmatic tendency."

Elsewhere in the paper it makes it clear that the mechanism postulated is that ETS is a co-factor *"operating with intercurrent infections."*

They summarized data from 13 studies of asthma severity and stated that *"due to the different approaches employed in each study, no formal meta-analysis is possible"* (a view one cannot dissent from), but a *"qualitative review … suggests greater disease severity in children exposed to smoking in the household, a pattern which is more consistent among asthmatics attending hospital as outpatients or inpatients than among cases identified through population surveys."* They also commented on the lack of adjustment for potential confounding in these studies and considered that *"some of the associations of parental smoking with health service utilisation, in particular, may reflect a common association with lower socio-economic status."* They also noted that the striking association of intubation with ETS exposure seen in the Davis study (LeSon & Gershwin, 1995) *"was stronger than that with a range of psychosocial variables, suggesting that it would not be entirely explained by socio-economic confounding."*

This review (Strachan & Cook, 1998b) also noted that the results of the early Minnesota study (O'Connell & Logan, 1974) are difficult to interpret. It also highlighted the change in the relationship between maternal smoking and asthma severity before and after July 1986 seen in the Vancouver study (Murray & Morrison, 1993). Like us, they are unconvinced by the authors' claim that this is due to an alteration in parental smoking habits following advice from clinicians to avoid smoking in the home or in the presence of the child, noting that this claim is based only on anecdotal reports and not on objective evidence.

The second relevant paper from the St George's Hospital Medical School Group, entitled *"Parental smoking, bronchial reactivity and peak flow variability in children"* (Cook & Strachan, 1998), concluded that *"A clear effect of exposure to environmental tobacco smoke on BHR in the general population has not been established. While the meta-analysis suggests a small but real increase in BHR in school aged children, it seems likely that this estimate is biased upwards due to publication bias. In contrast, limited evidence suggests greater variation in peak expiratory flow in children of smoking parents."*

These conclusions were mainly based on data for healthy children. Though some studies of asthmatics were cited, these were not clearly separated out in the tables summarizing the results. The authors noted that of five studies of the effect of ETS on bronchial hyperresponsiveness in asthmatic or wheezing subjects compared with normal subjects, two reported a stronger effect in asthmatics (O'Connor et al., 1987; Martinez et al., 1988), two reported a stronger effect in non-asthmatics (Strachan et al., 1990; Frischer et al., 1992) and one reported a similar association (Agudo et al., 1994). We have included only three of these five studies (O'Connor et al., 1987; Martinez et al., 1988; Frischer et al., 1992) in our review, the other two (Strachan et al., 1990; Agudo et al., 1994) being rejected for reasons discussed in section 5.1. The authors also noted a lack of significant association in asthmatic children with ETS exposure for peak variability (Frischer et al., 1993).

While the St George's Hospital Medical School reviews were relatively thorough, they gave little attention to the problem of confounding. Since their proposed mechanism hinged around ETS acting as a co-factor operating with intercurrent infection, it is all the more surprising that the authors have apparently not investigated at all the possibility of bias if

exposure to infections is greater in households with smokers, given the increased proneness of smokers to infections of various types (Arcavi & Benowitz, 2004). There was also no emphasis on the absence of data to distinguish potential effects of maternal smoking in pregnancy and of ETS exposure.

Another review was entitled *"Environmental tobacco smoke, indoor allergens, and childhood asthma"* (Gold, 2000). A brief section on *"ETS and exacerbation of asthma"* referred to previous reviews (National Cancer Institute, 1993; Strachan & Cook, 1998a) and to only a few of the relevant studies (Evans et al., 1987; O'Connor et al., 1987; Murray & Morrison, 1989). It highlighted the importance of acute respiratory infections in the exacerbation of asthma, but did not mention the problem of lack of control for such infections in the ETS studies. Nor were the difficulties of distinguishing ETS and *in utero* exposure discussed. The review concluded that ETS *"can exacerbate already established childhood asthma."*

A review on *"Environmental tobacco smoke and respiratory diseases"* (Jaakkola, 2000) included in its section on *"Severity of asthma"* a paragraph mainly summarizing the findings of other major reviews (Strachan & Cook, 1998a; National Cancer Institute, 1999). The author noted that *"due to highly variable outcomes, a formal meta-analysis was not possible to carry out,"* and concluded that *"several studies carried out all over the world provide strong evidence that ETS exposure is related to a more severe form of asthma and poor overall control of asthma in children ≤17 years."* The review summarized much of the available data on bronchial hyperresponsiveness and PEF variability, though when considering *"ventilatory lung function"* effects in asthmatics were not separated out. In the summary the author stated that *"Parental smoking causes asthma in children, and the evidence strongly supports its role in aggravating asthmatic symptoms."*

As noted in Chapter 4, the updated report of the California EPA (California EPA, 2005) included asthma exacerbation in adults in their list of *"Effects Causally Associated with ETS Exposure."* The same conclusion was reached for children. They described studies in children published since their original report (National Cancer Institute, 1999). Of these we rejected two (Willers et al., 2000; Gilliland et al., 2003) as the endpoint was not asthma, but the rest are considered in this report (MacArthur et al., 1996; Meijer et al., 1996; Abulhosn et al., 1997; Dubus et al., 1998; Oddoze et al., 1999; Schwartz et al., 2000; Li et al., 2000; Crombie et al., 2001; Ehrlich et al., 2001; Venners et al., 2001; Melén et al., 2001; Mannino et al., 2002). As with the original California EPA report (National Cancer Institute, 1999), many relevant references were missed. Even restricting attention to those epidemiological studies of asthma exacerbation and severity published between 1998 and 2002 which one would have expected to appear in the update, there were 15 omissions (Seidler et al., 1998; Wafula et al., 1999; Shamssain & Shamsian, 1999; El-Dahr et al., 2000; Güler et al., 2000; Ratageri et al., 2000; Gürkan et al., 2000; Al-Ghamdy et al., 2000; Mayo, 2001; Wilson et al., 2001a; Morkjaroenpong et al., 2002; Gaspar et al., 2002; Kalaajieh, 2002; Wamboldt et al., 2002; Dales et al., 2002), as against only the seven they considered. Clearly, their literature searching was inadequate.

While short summaries of the 14 new studies were included, the discussion and interpretation was very limited, the relevant section being reproduced below:

> "Taken together, the recent evidence supports the original 1997 Cal/EPA report's conclusion that ETS is a causal factor for asthma exacerbation among children. The cross-sectional

studies are all limited by the possibility of selection effects, such as smoking reduction by parents who have children with more severe asthma. This bias, which is unavoidable in cross-sectional studies, would attenuate any observed risk estimate. The longitudinal studies, which are less prone to this bias, are most consistent with an adverse effect of ETS on childhood asthma status, and consistently show elevated risk of symptoms, more and prolonged medication use, and increased school absenteeism. In addition, as shown in a recent meta-analysis by Vork *et al*., (2002), hidden environmental differences between studies may distort risk estimates. Specifically, higher ETS-related asthma risks were reported in areas with lower ambient air pollution. It was suggested that in polluted areas, individuals who are genetically more susceptible to asthma may be more affected by the ambient air pollution than by ETS, thus masking the effects of ETS exposure. If nondifferential, failure to account for the effects of ambient air pollution could bias risk estimates towards unity."

The report lacked any attempt to bring together all the relevant data relating to specific endpoints, so provided no good information on the consistency of the findings.

5.3.3. Conclusion

There are quite a substantial number of studies in asthmatic children which, taken together, suggest strongly that ETS exposure increases the risk of acute exacerbations. However the results are heterogeneous, and interpretation of the association is not completely straightforward, with failure to control for potential confounding variables, including maternal smoking in pregnancy. An effect on reduced lung function may exist, with the results most suggestive for $FEF_{25-75\%}$, but has not been clearly established. There is no consistent association of bronchial responsiveness with ETS exposure.

5.4. REFERENCES

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Chapter 6

EXACERBATION OF ASTHMA – OVERALL ASSESSMENT

Chapter 3 described the results of about 25 experimental chamber studies in which non-smoking asthmatic subjects were exposed to tobacco smoke for between 1 and 6 hours. Chapters 4 and 5 described, respectively, eight epidemiological studies in non-smoking asthmatic adults and 47 epidemiological studies in asthmatic children, in which ETS exposure was related to exacerbations of their condition.

The experimental chamber studies, particularly the series of studies in New Orleans, provide strong evidence that there is a proportion of asthmatics who react to exposure by a drop in FEV_1 of 20% or more. Reaction (and non-reaction) could be consistently demonstrated, and reaction was shown to be dose- and time-related. While some subjects only reacted at the higher doses tested, which were typically much higher than encountered even in extreme environmental conditions, a few reacted at even the lowest dose levels tested, which were more typical of high environmental exposure. Reaction to sham exposure was typically much rarer than reaction to the actual exposure. Though this exposure was often to sidestream smoke only, or to a mixture of mainstream and sidestream smoke and not strictly to ETS, it seems reasonable to conclude from these data that, in a subset of susceptible individuals, tobacco smoke exposure can exacerbate asthma, and also induce those symptoms (cough, chest tightness, wheezing, difficulty in breathing) which occur during an attack of asthma. It also seems that in the great majority of asthmatics, tobacco smoke exposure, even at extremely high concentrations, does not cause asthmatic attacks.

Four of the epidemiological studies in adults and 18 in children related ETS exposure to one or more lung function variables. There is no clear evidence in adults or children that ETS exposure was associated with reduced FEV_1, FVC or their ratio. The data for $FEF_{25-75\%}$ are more suggestive of an association with ETS exposure but are not completely consistent. Though five of the 10 studies of PEFR (all in children) reported some significant associations, the data are difficult to interpret, due to variability of endpoints, very incomplete reporting and inconsistency within some studies.

There is no consistent relationship of ETS exposure to bronchial responsiveness, investigated in one study in adults and seven in children.

There are a substantial number of studies which taken together suggest strongly that ETS exposure increases the risk of acute exacerbations. In the six studies in adults which reported

results for such endpoints as emergency department visits, hospitalisations, acute episodes and restricted activity days, all but one reported significant positive associations in at least one analysis. In children, the more extensive evidence allowed more detailed analysis by type of endpoint. The strongest evidence of an association was apparent for emergency room visits and urgent consultations (where four out of six studies reported significant positive associations), asthma severity (where six out of 13 did) and asthma symptoms and acute episodes (where seven out of 14 did). There was also some evidence of an association for hospitalisation, restricted activity and asthma medication. There are a number of issues that affect interpretation of the evidence. These include heterogeneity of the findings (with a few studies reporting very strong relationships and a number reporting no positive relationship at all), the lack of clear evidence that within-child increases in ETS exposure are associated with asthma exacerbations, limited reporting of relevant study details, and failure to control for potential confounding variables in many studies. The possible role of intercurrent infection has also not properly been accounted for. Whether or not ETS exposure can exacerbate asthma in all asthmatics, the findings certainly reinforce the evidence from the chamber studies.

Taking all the evidence together, we conclude that ETS exposure can exacerbate asthma, though not necessarily in all exposed individuals.

Chapter 7

INDUCTION OF ASTHMA – METHODS AND GENERAL CONSIDERATIONS

7.1. IDENTIFYING THE STUDIES

The objective was to identify epidemiological studies of case-control, prospective or cross-sectional design, which presented RRs relating any aspect of passive smoking to asthma induction, provided data from which such RRs could be calculated, or commented on the significance or non-significance of the relationship. Uncontrolled case studies were not included, as RRs cannot be calculated. Studies of asthma exacerbation were not included. As expected, no studies of asthma mortality were found.

Note that in the above paragraph and in the whole of the sections on asthma induction the term "RR" is taken to include not only direct estimates of the relative risk, but also indirect estimates based on odds ratios (ORs).

It was specified that only studies where the endpoint was "asthma" were to be included, with studies of "wheeze," "wheezing bronchitis," "chronic wheezing," "asthma or wheeze" or "asthmatic bronchitis" to be excluded. In practice this distinction was not always clear-cut, and it was decided that if the endpoint was called "asthma" by the original authors it would be included, even if on the basis of their more detailed description of the outcome it would have been excluded. This may have led to some anomalies. For instance, two studies may have used the same questionnaire-based list of symptoms to define the outcome. If one study merely described this as "asthma," that would be included, while the other study, describing it more accurately as, say, "asthma/wheeze syndrome" would be excluded. This strategy may have had the unfortunate effect of excluding some well-conducted studies, where the original authors deliberately avoided the use of the term "asthma" or deliberately included the term "wheezy bronchitis" because of local linguistic or diagnostic considerations. We made one exception, by including a study in children where the outcome was "attended physician for wheeze diagnosed as asthma or wheezy bronchitis," this outcome having been selected by the original authors (Fergusson & Horwood, 1985) on the basis of a published conclusion that the two conditions are indistinguishable (Williams & McNicol, 1969), with the results for asthma alone having been stated not to differ.

It was also originally specified that studies of children should be restricted to those aged up to 18. However, results were also included from prospective studies which recruited the

subjects when they were children and continued to follow them into early adulthood, and from cross-sectional studies where a small proportion of the subjects were aged over 18. For adults, only studies restricted to non-smokers, or presenting results separately for non-smokers, were included. No such criteria applied to studies of children.

Potentially relevant papers were identified from the extensive files on smoking and health accumulated by PNLSC and from Medline searches, using the strategy ("asthma"[MeSH Terms]) AND ("adult"[MeSH Terms]) AND ("tobacco smoke pollution"[MeSH Terms]) for chapter 8, with MeSH terms "adolescent," "child," "child, preschool," "infant" or "infant, newborn," replacing "adult" for chapter 9. For children, additional searches were also carried out replacing the "tobacco smoke pollution" term by "smoking" [MeSH Terms] AND ("maternal-fetal exchange" [MeSH Terms] OR "maternal behavior" [MeSH Terms] OR "pregnancy" [MeSH Terms]). Abstracts were examined and the apparently relevant papers obtained from the British Library.

Attention was restricted to papers published by the end of 2004, but no restriction was made on language. Translations were obtained of non-English-language papers, except in some cases where dictionaries were used to identify key information.

The next step was to take the papers that contained relevant data and classify them into the separate studies they described, taking account of the fact that some papers described results from more than one study, and some studies were described in multiple publications. Results available separately for different countries within a multinational study or for parts of a study having different study design features have been treated as belonging to separate studies. For each study identified, a file was built up of papers relevant to that study, the files being sorted by continent, by country within continent, and by state within the USA. This sorting made it easier to ensure that studies identified as separate really were so. On occasion, some studies were found which were not truly separate, for instance where some asthma cases are included in more than one study. These overlapping studies are discussed in §8.1.3 and §9.1.3.

For each relevant paper, and also for review papers covering the subject matter, reference lists of cited papers were studied to identify further relevant papers. Ultimately, a position was reached whereby no paper accepted for the study cited a paper of possible relevance that had not already been examined.

7.2. DATABASE STRUCTURE

For both children and adults there are two linked databases. In the first, known as the study database, there is one record per study, holding information relevant to the study as a whole and identified by a unique six-character reference (REF). The study database is described more fully in §7.4. The second database holds the detailed results, and can contain multiple records for each study. Each record refers to a specific comparison, and contains information describing that comparison (e.g. current smoking by the father vs no smokers in the household, for a particular sex, age, race and asthma type) as well as the actual results. Although it is known as the “RR database,” the results included are not restricted to RRs and may include indirect estimates of the RR, such as the OR, and also other statistics. Each

record also contains the study REF, which links it to the relevant record in the study database. The RR database is described more fully in §7.7.

7.3. DATA ENTRY AND CHECKING

Detailed instructions on the methods of data extraction and entry onto the databases were prepared by BAF and amplified as necessary as new problems were encountered in the course of carrying out the data entry. These are available in *www.pnlee.co.uk/etsast.htm* [Appendices 1, 2].

Before data entry, master copies of the papers in the study file were read through closely. Some studies were rejected at this stage because more detailed examination showed they did not actually meet the inclusion criteria. The information to be entered was identified and marked with highlighter pen (and notes made on the paper where necessary) to facilitate later checking. Where multiple papers were available for the same study, a principal publication was selected to provide most of the information, though details of interest not described in the principal publication but available elsewhere were also entered. The principal publication was usually that which provided information on the largest number of asthma cases, for example based on longer follow-up for a prospective study or avoiding interim results from a case-control study. Where descriptions of some study aspects conflicted between different papers, the most likely version was determined by consultation between the authors of this book, with notes of the problem recorded on the database.

Any preliminary calculations prior to data entry were made in Excel spreadsheets. The study data and the RR data, whether as given directly in the paper or as derived, were entered on the database by BAF. An automatic checking program which investigated the completeness and consistency of the data entered was run. (See *www.pnlee.co.uk/etsast.htm* [Appendices 3, 4] for details of the automated checks.) A full printout of the data for each study was then produced and PNL checked both the calculations and data entry against the original papers.

To maintain consistency of data entry, the checking stage by PNL was not started until many of the studies identified in the first phase had been entered by BAF, so ensuring reasonable confidence that further changes to the data entry instructions would not be needed. Where a new paper was identified relevant to a study that had already been entered, the original data entry was rechecked in the light of any additional information.

7.4. STRUCTURE OF THE STUDY DATABASE

The study database structure is outlined here and described in more detail in *www.pnlee.co.uk/etsast.htm* [Appendices 5, 6]. It contains one record per study. Each record is uniquely identified by a six character study reference, usually based on the principal author's name.

Each record consists of "fields" within "cards." The cards separate the different main classes of information recorded, while the fields contain the individual data items within each

class. Data items may be entered as missing or not applicable. The six cards used for data entry, together with a brief description of the fields included in each, are as follows:

- *Study description.* This card includes the study short and full title, details of possible overlaps or links with other studies on the database, whether the study is restricted by gender or is unrestricted, the age range and the race of the population considered, the location of the study, the period of the study, the year and reference key of the principal publication and the reference keys of any other publications. A free-text comment also contains additional detail where required, particularly concerning overlapping studies.
- *Study design.* This card includes the study type (case-control, prospective, or cross-sectional), the type of controls used (e.g. healthy, diseased/hospital), the type of population studied (e.g. general population, farmers, schoolchildren, children with family history of allergy). It also includes details on the source of the ETS exposure data, whether this was ascertained by questionnaire (and, for studies in children, whether from the parents or the child) or by biochemical measurement. A free-text comment also contains additional detail where required.
- *Asthma.* This card includes two fields, indicating whether results are presented for lifetime asthma and for current asthma. For prospective studies, incident asthma is recorded in the "lifetime" field. The card also includes further fields giving the source of the asthma diagnosis, the timing of the asthma and a text field giving the detailed definition of the asthma. For current asthma, it is also recorded whether the asthma was restricted to first occurrence and, in prospective studies, whether current asthma was measured on more than one occasion. The card also includes the number of asthma cases and the total number of subjects included in the study.
- *Matching factors.* For case-control studies, this card includes which matching factors were used.
- *Confounders considered.* The first field of this card gives the total number of potential confounding variables considered for all the RRs entered in the RR database. The remaining fields indicate whether adjustment has occurred for each of 29 separate potential confounders. On most occasions, data entry for a confounder is 0 if it is not adjusted for or 1 if it is. Exceptionally, a higher number than 1 indicates that the confounder was adjusted for by use of more than 1 variable (e.g. family medical history by several specific conditions). A further field indicates that other potential confounding factors were formally considered but rejected (e.g. in a stepwise multiple logistic regression model) and these factors are listed in a free-text comment.
- *Other results.* This card records the availability of various data which have not at present been entered on the database. The first field indicates whether the study provides data on other definitions of asthma, which could have been used in this review in place of the outcome(s) chosen. The second field indicates other outcomes related to asthma which would not have qualified for this review, such as wheeze. Further fields indicate, as appropriate, the availability of results for other ETS exposure indices (such as smoke exposure outside the home, or changes to parental smoking habits), of results for active smoking in the child database, of results using

other definitions of non-smoking (including ex-smoking) in the adult database and of results stratified by other factors or restricted to subsets of the study population.

7.5. STUDY REPORTS

The data recorded on the study database for each study are presented in the form of a computer-generated report (see *www.pnlee.co.uk/etsast.htm* [Appendices 11, 13]).

7.6. PROBLEMS WITH OVERLAPPING STUDIES

In theory, RRs being meta-analysed should come from independent studies involving distinct asthma cases; if some asthma cases feature in more than one study, they will be "double-counted" in any meta-analysis which includes results from both studies. In practice, avoidance of such double-counting is difficult and may not always be the most desirable solution. For example, suppose study A describes a cross-sectional study conducted in 1970 involving all primary school children (age 5-11) in a particular town, while study B describes a similar cross-sectional study in the same town conducted in 1975. Including results from both studies would involve some double-counting (i.e. of children aged 5-6 in 1970 and 10-11 in 1975), but avoiding this would require totally ignoring results from one study (or both), with a substantial loss of power, which would seem to be less desirable than allowing some double-counting. Even omitting study B if it had been conducted in 10-11 year-olds (totally within the population of study A) may not necessarily be appropriate, if the paper describing study B reports data for some exposure indices not considered in the paper describing study A. One would not want to include results from both studies in analysis of the same exposure index (and would omit study B if both RR estimates were available), but one might want to use data from either study if only one provides the required RR. There are other possibilities too that need to be borne in mind; for example, studies of overlapping regions or studies which do not completely describe where or when they were conducted and may overlap other studies.

In entering data from individual studies, care was taken to avoid double-counting by, for example, not entering results for the same exposure index for all cases and for a study subset. Nevertheless, there were some sets of studies which were noted on the database as having overlaps or links. For the purposes of analysis, these sets of studies were grouped into two categories. The first category consists of studies with a modest degree of overlap which cannot be disentangled, where it was decided to ignore the overlap. The second category contains sets of studies which clearly do overlap, where one member of the set ("principal study") contains the most appropriate data and where, for other members ("subsidiary studies"), RRs should only be included in meta-analyses if equivalent results are not available from the principal study. These are described further in §8.1.3 and §9.1.3.

7.7. Structure of the Relative Risk Database

The RR database is outlined here and described in more detail in *www.pnlee.co.uk/etsast.htm* [Appendices 7, 8]. It contains one record for each RR. The record includes the six character study reference linking it to the corresponding record on the study database, and a set of fields within cards. The four cards used for data entry, together with a brief description of the fields included in each, are as follows:

- *RR description.* This includes an RR identification number which is unique within the study, together with details defining the RR. These include the sex, age range, race, asthma type (lifetime or current) and, for prospective studies, whether the analysis was of prevalence or incidence. The passive smoke exposure is defined by type (for studies of children: parental [including *in utero*], household, total, whether biochemically assessed, or a combination with *in utero*; for studies of adults: household, workplace, total, whether biochemically assessed), specific source within the family, and time of exposure, together with similar information about the unexposed base, or details of the biochemical assessment. The source of the RR (including reference key, table and page numbers) is also given.
- *RR adjustment.* This includes whether or not the RR is adjusted for sex, age, race, other aspect of passive smoking or other confounders, and in the case of other confounders, the number of variables adjusted for. The actual number of other confounders adjusted for is given in a text comment if the set is less than the full set already defined in the study database.
- *RR data.* This includes the numbers of exposed and unexposed cases. For unadjusted results only, it also includes the numbers of exposed and unexposed controls or disease-free subjects for prevalence analyses, or the at-risk population or person-years at risk for incidence analyses. For all results, it includes the RR estimate itself and its upper and lower 95% confidence limits. For unadjusted data the RR and 95% confidence limits are calculated from the 2×2 table (if available). For adjusted data, they may be as given in the source papers or as derived by other means, a further variable indicating the method of derivation. The possible methods of derivation are described in §7.9.
- *Discrepancy.* Any alternative discrepant results are noted here, as are results adjusted for alternative variables.

7.8. Identifying which Relative Risks to Enter on the Database

In identifying what RRs to enter, four aspects – passive smoking index, asthma type, confounders adjusted for, and strata – were considered and these are discussed in the following sections. RRs relating to all combinations of these aspects were entered.

For studies of children, RRs entered were, if available, for non-smokers and otherwise for all children (including smokers, if any). RRs restricted to smoking children were not entered.

For studies of adults, RRs entered were, if available, for never smokers and otherwise for non-smokers.

As discussed earlier (§7.6), it is important in meta-analyses to avoid "double-counting," and this applies equally within studies. In some circumstances it is quite legitimate for more than one RR from a study to be included in a meta-analysis; for instance RRs by sex or non-overlapping age groups. In other circumstances it is not legitimate. For example, if maternally exposed and paternally exposed subjects were each compared to those with no smokers in the family, including both in a meta-analysis of parental smoking would double-count the unexposed group. Also if current asthma is measured repeatedly in a cohort and analysed at successive attained ages, then the estimated RRs will not be independent. For a simple stratifying variable, it is readily apparent at the analysis stage whether or not inclusion of multiple RRs is valid. However, in other cases it is not. It was therefore decided that, with the exception of the straightforward strata of sex, all valid combinations would be constructed at the outset. This resulted in a larger, and sometimes considerably larger, number of RRs being entered for some studies than had been presented in the original papers.

7.8.1. Passive Smoking Indices for Children

Passive smoking exposure was either based on questionnaire responses or on biochemical assessment.

Questionnaire-based exposure

For questionnaire-based exposures, it was necessary to define the exposure of the numerator and of the denominator separately for each RR. Exposure was defined according to whether it was from smoking by parents or other household members, or from total exposure, with details also recorded to clarify the specific source (who specifically smoked), amount and timing of the exposure. This is described further below.

When identifying the numerator, exposure was restricted to one of four types:

1 parental – active smoking by the parents, whether specified as being in the presence of the child or not
2 parental ETS – passive smoking by parents (in practice this refers only to exposure of the mother during pregnancy)
3 household – smoking by household members (except as already covered by parental smoking), or smoking in the home (i.e. including smoking by visitors), again regardless of whether or not in the presence of the child,
4 total exposure – exposure either inside or outside the home, or unspecified exposure

Results for other types of exposure were not entered.

For parental (and parental ETS) exposures, one of the following levels was additionally selected to indicate who smoked (or was exposed):

1 mother and not father
2 mother, irrespective of father's smoking
3 father and not mother
4 father, irrespective of mother's smoking
5 both parents
6 any parent (i.e. mother and/or father)
7 one parent but not both

If a study found no smoking mothers, results for paternal smoking were entered twice, with both levels 3 (father only) and 4 (father irrespective of mother).

For household smoking, the sources available varied between studies, and were entered as found in the original paper. As well as "any household member," levels included siblings, grandparents, and any household member other than the parent(s). Similarly for total exposure, the levels found included "home and peers," and "home and daycare."

The timings of the exposure also varied between studies, and were entered on the database as found. They included times related to the child's gestation/lifetime (before conception, during gestation [*in utero*], during lifetime, during gestation and/or lifetime, at a specific age, before a specific age), times related to the smoker's lifetime (parent/household member is an ever smoker, or an ex-smoker, or ever smoked but did not smoke during pregnancy), current or recent times, and unspecified timing.

The RR is further described as relating to the whole exposed group so far defined (e.g. current maternal smoking) or to a level of exposure within that group, whether by number of cigarettes exposed to (or smoked by the smoker in question) (e.g. 1-10, 11-20, etc. per day), minutes per day of exposure, number of persons smoking in the household[2], or a semi-quantitative level (e.g. occasionally). The categories used vary considerably from study to study, and have been entered as given in the original paper. An open-ended group is coded as 999.

When identifying the denominator, attention was restricted to five groups:

1 no exposure at all
2 no household exposure
3 no exposure from the specified household member
4 no parental exposure
5 no exposure from the specified parent

with only level 1 relevant for total exposure, and only levels 1-3 relevant for household exposure. If "no" exposure was not available as a denominator, then "no or low" exposure may have been used. The denominator is further defined as:

1 not at the time defined for the numerator
2 never smoked (only relevant when the numerator refers to current/former/ever smoking by a parent/household member)
3 not at the time defined for the numerator and not at some additional time

[2] Number of parents smoking was not specifically entered as a dose response, but the levels "one only" and "both" can be interpreted as such.

Generally, all valid combinations of the above definitions of numerators and denominators were entered, even if not specifically given by the original authors. Thus, for example, if data were available for the following parental smoking exposure groups:

A none
B mother only smokes
C father only smokes
D both parents smoke

then RRs would be entered for:

B vs A	mother only	vs	neither parent	
C vs A	father only	vs	neither parent	
D vs A	both	vs	neither parent	
B+C vs A	one (not both)	vs	neither parent	
B+D vs A	mother (+/-father)	vs	neither parent	
C+D vs A	father (+/-mother)	vs	neither parent	
B+C+D vs A	any parent	vs	neither parent	
B vs A+C	mother only	vs	not specified parent	
C vs A+B	father only	vs	not specified parent	
B+D vs A+C	mother (+/- father)	vs	not specified parent	
C+D vs A+B	father (+/-mother)	vs	not specified parent	
B vs A & D vs C	mother (+/- father)	vs	not specified parent	adjusted for father
C vs A & D vs B	father (+/-mother)	vs	not specified parent	adjusted for mother

However “both parents” vs “one or no parent” would not be entered. For household smoking, the comparison of “any household exposure” vs “no household exposure” would be constructed if possible, but otherwise only the RRs as originally given would be entered.

Also, if exposure data were available as never, current and former smoking for any specified source person, then RRs would be entered for:

current vs non
current vs never
ex vs never
and ever vs never.

Note that ever smoker versus non-smoker would not be a valid comparison, as ex-smokers would be counted in both the numerator and denominator.

Biochemically assessed exposure

All results for biochemically assessed exposure were entered, with the source (saliva, blood etc), the biomarker measured (cotinine, CCR etc), and the value used to distinguish between unexposed and exposed all noted in the database.

Combination Exposures

Where a study gave results for combinations of *in utero* exposure and one of the above mentioned exposure types in lifetime, relative to neither exposure, this was entered as three RRs with a special exposure type (designated e.g. "*in utero* × parent"), and further qualified by a field with levels "0-1," "1-0" and "1-1" indicating the comparison. Aspects of the lifetime component of these combinations (source, time, amount, denominator) were then entered on the database in the same way as for a simple exposure (identically for the three RRs). The *in utero* component of the combination was not further defined on the database, but was taken as referring to maternal smoking during pregnancy.[3]

For instance, if results were available for the following exposure groups:

		Father smokes currently	
		No	Yes
Mother smoked in pregnancy	No	A	B
	Yes	C	D

then RRs would be entered for B vs A, C vs A, D vs A, each with exposure "*in utero* × parent" but having levels "0-1," "1-0," "1-1" respectively. Each RR would be further defined by source = "father irrespective of mother," time = "current," amount = "all" and denominator = "not the specified parent."

7.8.2. Passive Smoking Indices for Adults

For questionnaire-based exposures, it was again necessary to define the exposure of the numerator and of the denominator separately for each RR. Here, exposure was defined according to whether it was from household members smoking or from workplace or total exposure, with details again recorded, as appropriate, on the specific source, amount and timing of the exposure. The way exposures are defined in the RR database is similar to that for childhood exposures (see §7.8.1). No results were found for maternal smoking in pregnancy (*in utero* exposure).

The only results found for biochemically assessed exposures refer to serum cotinine.

7.8.3. Asthma Type

Results were entered for lifetime, incident and current asthma, as defined in the study database.

[3] It was later realized that for two studies (AGABI1, AGABI2), for combinations of *in utero* and paternal smoking in lifetime, the *in utero* component also referred to paternal smoking, i.e. effectively to passive smoking by the mother during pregnancy.

7.8.4. Confounders Adjusted for

Results were entered unadjusted, and adjusted for the most confounders for which results were available. If the confounders included other aspects of passive smoke exposure as well as other confounders, then results adjusted for the other confounders but not for the other passive smoke exposure were also entered.

7.8.5. Strata

Three strata were considered – sex, age and race. Results were entered for males and females separately when available. Combined-sex results were only entered when the equivalent single-sex results (i.e. for the same passive smoking indices, confounders, age and race) were not available. For children results were entered both for all ages combined[4], and for individual age groups, the age groups used varying considerably from study to study. Results were also entered for children for all races and for individual racial groups. For adults, no results stratified by age or race were found.

7.9. DERIVATION OF THE RELATIVE RISKS

Unadjusted RRs were calculated from their 2 × 2 table, if available, and otherwise were entered as given. If the numbers of cases are denoted by a_i and the numbers at risk (or person-years at risk) in an incidence study by b_i, where the subscript $i = 0$ refers to the unexposed group and $i = 1$ refers to the exposed group, then the RR and its lower and upper confidence limits (LCL and UCL) were estimated by:

$$RR = (a_1\, b_0) / (a_0\, b_1)$$
$$LCL = RR / \phi$$
$$UCL = RR\ \phi$$

where ϕ, a factor based on the variance of the logarithm of RR, is given by

$$\ln(\phi) = 1.96\sqrt{((1/a_0) + (1/a_1) - (1/b_0) - (1/b_1))}$$

For a case-control study, b_i denotes the controls, and for a cross-sectional study b_i denotes the disease-free subjects, and the formulae to calculate the RR (as estimated by the OR) and its CI are the same, except that

$$\ln(\phi) = 1.96\sqrt{((1/a_0) + (1/a_1) + (1/b_0) + (1/b_1))}$$

[4] This does not apply to repeat measures of current asthma in prospective studies

If both a 2 × 2 table and an unadjusted RR/CI were presented originally, then the RR/CI calculated as above is used, and any discrepancy from that originally given is noted in the database.

The 2 × 2 table may be constructed by summing groups (e.g. adding current and ex-smokers to obtain ever smokers, or adding over other stratifying factors), or from a percentage distribution.

Adjusted RRs and their 95% CI were entered as given when available. For an incidence analysis, the odds ratio is used only if the RR is not available (typically when estimated from a multiple logistic regression), and this is noted in the database.

A variety of other methods were used to provide estimates of the RR and CI in other circumstances. The main methods are described briefly here, and fuller details are available from *www.pnlee.co.uk/etsast.htm* [Appendix 9]. Calculations were mainly carried out using Excel spreadsheets.

Correction for zero cell. If the 2 × 2 table has one cell with value zero, the RR and CI cannot be calculated by the usual formula. The method used is to add a correction of 0.5 to each of the four cells, and then apply the formula.

Combining independent RRs. Combining RRs over strata uses the method of Fleiss & Gross (1991), the same method as for fixed effects meta-analysis. The resulting estimate is adjusted for the stratifying variable. When this combined RR is subsequently used in a meta-analysis, the end result will be exactly the same as if all the original RRs had been included. This method is also appropriate for combining RRs for individual disease groups, provided they are independent estimates (i.e. each disease group has a separate control group).

Combining non-independent RRs. When non-independent RRs are to be combined, then the method of Fry & Lee (2000) is used, for instance if adjusted RRs are available for parent current and ex- smokers, each versus never smokers, to provide a combined estimate for ever smokers. This method starts from a source table giving adjusted RRs and CIs for n exposed groups relative to a single non-exposed base group. The hypothetical underlying $2 \times (n + 1)$ table of numbers of "adjusted cases and controls" is estimated, these then being summed to give the required groups for the numerator and denominator, and the resulting 2 × 2 table used with the usual formula to estimate the adjusted RR and CI. A variation of the method allows non-independent disease groups to be combined. Thus when RRs for several disease groups are given, each relative to a single shared control group, the disease groups can be combined, or one disease group (e.g. asthma) can be compared with a combination of another disease group (e.g. wheeze without asthma) and the control group.

CI estimated from p-value. When an adjusted RR was presented originally without a CI but with a p-value, then the original RR is used and its CI is calculated using the formula

$$\ln(\phi) = 1.96 \ln(RR) / ND$$

where ND is the standard normal deviate corresponding to the p value.

CI estimated from crude numbers. When an adjusted RR was presented originally without a CI or p-value, but the corresponding 2 × 2 table is available, then the original RR is used and its CI is estimated by assuming its width is the same as the width of the interval for the equivalent unadjusted RR. In fact, the estimated interval will be narrower than the true one (since adjustment widens the interval [Lee, 1999]), and thus this method will increase the

weight that the estimate is given when entered into a meta-analysis. However this will usually be a small effect and the only alternative is to omit the RR altogether from all meta-analyses.

Checking the RR against the CI. Where appropriate, the centrality of the RR in the CI was checked using the statistic

$$C = (RR^2) / (UCL \times LCL)$$

which should have the value 1.0, though small departures from 1.0 are to be expected, particularly when the RR and CI are given to only one decimal place.

7.10. CARRYING OUT META-ANALYSES

7.10.1. Process of Selecting the Relative Risks for the Meta-analyses

The process of selecting which RRs to include in an analysis is described below in relation to the data for children, but was in fact the same for adults. The process can be quite complex as it has to address two main objectives – to include all the relevant data but at the same time to avoid double-counting. The rules used when entering data will ensure that double-counting is avoided if (1) within each study, values of the stratifying fields (sex, age, race) are non-overlapping; (2) within each strata only one value is chosen for each of: the passive smoke exposure index, the asthma type, the follow-up period and the number of confounders adjusted for; and (3) either a principal study or its subsidiary but not both are included.

When defining the relevant data for a particular analysis, it may be possible to choose a single specific value of a passive smoke exposure index (e.g. for an analysis of mother only smoked). Only RRs with that value will be included, and studies without any such RRs will be excluded altogether. However more commonly, a number of values may be acceptable in the analysis (e.g. in an analysis of parental smoking, RRs for either parent smoked, mother smoked, and father smoked may all be acceptable). An order of "preference" is defined, so that one value only will be chosen from those studies which had RRs entered for more than one acceptable value. In a similar way, preferred values of asthma type can be chosen, and the number of adjusting variables can be chosen to be the minimum or maximum available.

The choice between principal and subsidiary studies can be specified in a similar way, except that the preference is now implemented over the group of linked studies. RRs from the subsidiary study will only be allowed if there are no eligible RRs from the principal study.

For the stratifying variables of age and race, RRs may have been entered on the database for the whole study, or for individual strata, or both. For many analyses, results for the whole study will be preferred if available. However where only strata-specific RRs are available then the widest available strata will be preferred. For example, if a study included children of ages 5-14, but reported parental smoking results only for ages 9-14, and moreover additionally presented these results split into age groups 9-10, 11-12 and 13-14, then an analysis of parental smoking irrespective of age would choose the RR for age 9-14, whereas an analysis restricted to children aged up to 13 would include the two RRs for ages 9-10 and 11-12.

When specifying preferences on a number of fields, the order in which they are implemented may affect the outcome. For instance, suppose an analysis of maternal smoking is required. The exposures "maternal smoking (regardless of paternal smoking)" and "maternal smoking only" are defined as first and second preferences respectively, as are asthma types "lifetime" and "current." Further supposing that a study has two RRs, (1) for "maternal smoking (regardless of paternal smoking)" and "current" asthma, and (2) for "maternal smoking only" and "lifetime" asthma. If the preference on maternal smoking were implemented first, then RR 1 would be chosen, whereas if the preference on asthma type were implemented first, then RR 2 would be chosen. Therefore, attention is first restricted to those RRs which have acceptable values for all the preferencing fields. Preferences for the most important aspects of the analysis, usually the passive smoking exposures, are implemented next, while the less important aspects, usually the demographic strata and the principal/subsidiary study status, are implemented later.

It was decided at the outset that single-sex results would be preferred to combined-sex results, and the latter have only been entered on the database when the former are not available. For single-sex results, the passive smoking results that are available are sometimes different for the two sexes (e.g. a principal study may present only male results while a subsidiary has results for both sexes, or a study may present unadjusted results for the separate sexes but adjusted results only for sexes combined). For these reasons, all setting of preferences is done within sex, and then the choice between sex-specific or sexes-combined is implemented afterwards.

7.10.2. Combining the Relative Risks

The method used to carry out the meta-analysis of the selected RRs, again the same for children as for adults, is as described by Fleiss & Gross (1991). Both fixed effects and random effects meta-analysis have been carried out to form combined estimates of the individual independent RRs. Fixed effects meta-analysis assumes a common underlying RR estimate and only takes into account within-study variability in calculating the combined RR estimate and its 95% CI. Random-effects meta-analysis also takes into account between-study variability. Where there is no evidence of heterogeneity between the sets of estimates, the two analyses give the same results.

The notation used in some of the output is the same, where relevant, as that used by Fleiss & Gross (1991). Thus, we have:

N	the number of RRs being combined
NS	the number of studies from which the RRs are taken except that when the analysis is subdivided into factor levels (see §7.10.3) NS in the Total column is the sum of the values in the individual columns, i.e. the number of study × factor levels from which the RRs are taken
s	the individual RR estimate being combined (s = 1, …N)
Y_s	the logarithm of RR_s
W_s	the associated weight, calculated as the inverse of the variance of the logarithm of RR_s
Wt	the total weight for all the RRs being combined

Fixed RR	the fixed effects RR estimate, calculated by exp $((\sum W_s Y_s)/(\sum W_s)) = \exp(\overline{Y})$ summation being over s = 1, … N
Fixed RRl	the lower 95% confidence limit of the fixed effects RR estimate, calculated by $\exp(\overline{Y} - 1.96/\sqrt{\sum W_s})$
Fixed RRu	the upper 95% confidence limit of the fixed effects RR estimate, calculated by $\exp(\overline{Y} + 1.96/\sqrt{\sum W_s})$
Fixed P	the probability value associated with the fixed effects RR estimate, given in coded form as +++, --- p<0.001; ++, -- p<0.01; +, - p<0.05; (+), (-) p<0.1; N.S. (not significant) p≥0.1. Plus signs indicate the RR is significantly greater than 1.0, minus signs that it is significantly less
Q_s	the contribution to the heterogeneity estimate, calculated by $W_s(Y_s - \overline{Y})^2$. Where N is large, this can be regarded approximately as a chisquared on 1 d.f.
P_s	the associated probability value, used to indicate outliers, coded as for Fixed P
Het Chi	(or Q in Fleiss & Gross notation) the heterogeneity chisquared on N-1 d.f., calculated by $\sum Q_s$. If $Q \leq N-1$, the random effects and fixed effects estimates are the same, but if $Q > N-1$ they differ.
Het df	the degrees of freedom corresponding to Het Chi (= N-1)
Het P	the probability value associated with Het Chi, and Het df, coded as for Fixed P
Random RR, Random RRl, Random RRu	The random effects RR estimate and its lower and upper 95% confidence limits. The method for deriving this, originally described by DerSimonian & Laird (1986), is most conveniently given by Fleiss & Gross (1991)
Random P	the probability value associated with the random effects RR estimate, coded as for Fixed P
Asymm P	the probability value associated with Egger's test of publication bias (Egger et al., 1997) coded as for Fixed P. Only presented for analyses not subdivided by factor levels
Between Chi	where the meta-analysis is subdivided by levels of a factor, this is the chisquared value for the difference between the fixed effects RR estimates for the factor levels
Between df	the degrees of freedom corresponding to Between Chi, equal to the number of factor levels minus 1
Between P	the probability value associated with Between Chi and Between df, coded as for Fixed P except that asterisks indicate non-directional significance

7.10.3. Layout of Output

Meta-analysis tables are presented at the end of the relevant chapter. Each table consists of a preamble followed by the body of the table.

The preamble shows

(i) restrictions on the data included,
(ii) the order of preference for selecting RRs to be included, and
(iii) a short description of the contents of the table

The body of the table gives the results of fixed effects meta-analyses of the adjusted data, i.e. with RRs adjusted for the most potential confounders chosen from each study. For the overall data and for data subdivided by various factors, the output indicates, for each factor level, the number of estimates combined (N), the coded P value (as described in §7.10.2) testing for heterogeneity, the RRs and CIs themselves (RR, RRl, RRu, P) and, shown in the column for the first factor level, the coded P value for variation between factor levels. For the first analysis, of the overall data not subdivided by levels of any factor, the number of studies from which the estimates come (NS), the combined weight for the studies (Wt), results of random effects meta-analyses and coded P values for Egger's test of publication bias (Asymm P, Egger et al., 1997) are also given.

Fuller versions of all the meta-analysis tables are available at *www.pnlee.co.uk/etsast.htm* as Appendix Tables, together with a full description and list in Appendix 10. In each case, the Appendix Table contains the same preamble as the corresponding Table, followed by three sections giving details of the adjusted analysis. Sections 1 and 2 list various aspects of the data from the individual RRs included. Section 3 gives results of the adjusted meta-analysis and corresponds directly to the body of the Table, with the addition of the random-effects estimates of the RR and CI. (The test for variation between factor levels is shown here in the "Total" column.) Sections 4-6 of the Appendix Table then give similar lists and results for the unadjusted analyses (i.e. with RRs adjusted for the least confounders chosen from each study), while section 7 (and section 8 – children only) give information on excluded studies and on any results which would have been included in preference except that they had incomplete data (typically an RR without a CI).

Due to the large number of meta-analyses carried out, key tables are presented in the book, with others presented only in the Appendix Tables. The numbering of the Tables is consistent so, for instance, Table C3 (a key table) corresponds to Appendix Table C3 while Table C4 is not presented in the book but can be found in full as Appendix Table C4.

For selected meta-analyses, a forest plot is shown. For each estimate included, referenced by the study short name and sex (except where the estimate is for the sexes combined), the RR is shown as a rectangle, the area of which is proportional to the weight of the RR. The CI is indicated by a horizontal line. The RRs and CIs are plotted on a logarithmic scale so that the RR is centred in the CI. Also shown in the plot are the actual values of each RR and CI and the weight as a percentage of the total. Results from a random effects meta-analysis are shown at the bottom of the plot. These include the RR, CI, heterogeneity chisquared, degrees of freedom (df) and heterogeneity p value. The combined estimate is presented as a diamond with the width corresponding to the CI, and the RR as the centre of the diamond.

7.10.4. General Restrictions to the Analyses

The analyses carried out all satisfy the following conditions for selecting RRs, though not all are relevant to the data for adults:

- *Results complete enough for use in meta-analysis.* Adjusted RRs with no CI are excluded. Where a 2×2 table has a zero, the RR and CI is calculated by adding 0.5 to each cell of the table. In practice, whether or not such data are included in meta-

analyses makes little difference to the results as a RR calculated with a 0.5 in one cell has a large SE and therefore little weight;

- *Follow-up period for whole study or longest available*. This applies only to prospective studies. Where case-control studies present both interim and final results, only the final results are included on the database anyway (except if the interim reports give results relating to comparisons not considered in the final report);
- *Race all or nearest available.* Results are chosen for the whole population (or nearest available). Otherwise results are chosen by separate racial group;
- *Principal rather than subsidiary studies.* See §7.6 for a discussion of the problem of overlapping studies and the definition of "principal" and "subsidiary" studies;
- *Age*. Whole study if available, otherwise by widest available age group; and
- *Sex.* Single-sex results rather than combined-sex results.

7.10.5. Defining the Outcome and the Exposure

There is considerable choice as to the outcome and the exposure when selecting the RRs to be included in the meta-analysis.

- *Outcome.* "Lifetime asthma" is present if, at the time of interest (time of interview for case-control or cross-sectional studies, or time of follow-up for prospective studies) the subject has ever had asthma, while "current asthma" is present if the subject is considered to be asthmatic at the time of interest. Assuming that people are not asthmatic at birth, lifetime asthma is equivalent to induction of asthma by the time of interest. The main outcomes considered for meta-analysis are lifetime asthma and current asthma, and some meta-analyses are restricted to those studies which provide results specifically for the definition chosen. However since some, but not all, studies give results for both definitions, some meta-analyses are also carried out for lifetime asthma if available but for current asthma for those studies where lifetime is not available, this outcome being referred to as "lifetime/current asthma." Some meta-analyses are also carried out for "current/lifetime asthma" which is similarly defined but in the opposite order. All studies are eligible to contribute to such an analysis, so these outcomes may be preferred when looking at aspects of exposure for which few studies provide results. Some meta-analyses in children are restricted to those studies where the definition of asthma required that it had been diagnosed by a physician (whether obtained from medical records or as reported by either the child or a parent). Some meta-analyses in children are restricted to those studies which carried out an analysis of the onset of asthma (rather than prevalence), but there are very few such studies. In order to address the question of whether risk may vary with age, some meta-analyses in children are restricted to results which refer to those aged under 10, to those in an age group which includes 10, and to those aged over 10. Studies which did not provide age-specific results would be eligible to enter only one of these meta-analyses at most, whereas studies which provided results for several age groups may appear in more than one.

- *Source of exposure to ETS.* Four main sources of ETS exposure are meta-analysed. For *total exposure (or nearest available)*, biochemically-assessed exposure is chosen if available from a study, otherwise questionnaire-assessed total exposure is chosen; failing that, results for any household exposure, any parental exposure, maternal or workplace exposure, or finally paternal exposure are accepted in that order of preference. For *parental exposure* (a main source only for child analyses) the order of preference is any parental exposure (i.e. mother and/or father smokes), maternal (i.e. mother smokes irrespective of father), maternal only (i.e. mother smokes but father does not), paternal and paternal only. In addition, some meta-analyses are carried out for specific sources of exposure. For *household exposure* (a main source only for adult analyses) the order of preference is any household exposure or maternal (i.e. mother smokes irrespective of father's smoking). Some meta-analyses are carried out using paternal exposure in preference to maternal. The other main source of exposure, applicable only to adults, is *workplace exposure*.
- *Timing of exposure.* Exposure during the child's lifetime is considered in detail in § 9.3.1 and 9.3.2. Studies which gave results only in terms of the smoker's lifetime (e.g. whether the mother was an ever or never smoker, irrespective of whether any smoking coincided with the child's lifetime) are also considered there, as are studies of exposure at the time of birth. Usually the exposure chosen for meta-analysis is that referring to exposure during the child's whole lifetime, or the nearest available. This is chosen from those available from each study in the following order of preference: in-life (i.e. since birth); ever (i.e. in the life of the smoker); unspecified; in-life and/or in utero (i.e. since conception); at a specific age (including at baseline for prospective studies); current, and is referred to as "general" exposure. Meta-analyses are also carried out using alternative orders of preference favouring the most recent exposure available, or the exposure earliest in the child's life. In addition, separate meta-analyses are carried out for exposure which has discontinued (e.g. when the mother is an ex-smoker). Exposure *in utero* is also considered separately in §9.3.3 and 9.3.4, while joint assessment of exposure *in utero* and/or in-life is considered in §9.3.5.

  For adults the exposure usually chosen for meta-analysis is that referring to the earliest exposure during the subject's lifetime in the order of preference: childhood, lifetime, adulthood, recent, unspecified, current. Meta-analyses are also carried out using an alternative order of preference favouring the most recent exposure. Separate meta-analyses are also carried out for exposure specifically in childhood.
- *Definition of the unexposed comparison group.* Generally, the unexposed group chosen is as near as possible to the reciprocal of the exposed group, both in terms of the source of exposure and the timing of exposure. (This is referred to as the "most" unexposed, both because the most subjects are eligible for inclusion and because they have the most exposure.) Alternative meta-analyses are also carried out choosing the least exposed comparison group. Thus if, for instance, in a meta-analysis of maternal smoking, a study has three RRs for current exposure, where the comparison group is "mother not current smoker," "mother not smoked since child's birth" or "neither parent smoked since child's birth" respectively, then for the "most" unexposed analysis the result comparing with "mother not current smoker" would be chosen,

while in the "least" unexposed analysis, the result comparing with "neither parent smoked since child's birth" would be chosen.

Clearly if meta-analyses were conducted for all possible combinations of the four aspects considered in the previous paragraphs, the number of such analyses would be enormous. Consequently, most attention has been given to certain key analyses, with fuller output produced for them. Other analyses involve variation in the definitions from the key analyses, and produce a more limited output, which includes examination of the number of studies for which the change in the definition of the analysis actually changed the RRs included. The number of RRs which actually differ between a key analysis and a variant analysis is often quite small, or even zero, because many studies do not offer RRs for any alternative definitions of exposure/non-exposure. The number of RRs differing will also tend to be smaller when the key analysis used a wide ranging definition of exposure than when it uses a narrow one. For instance, if a key meta-analysis refers to total exposure with "most" non-exposure, then for any study which looked at various sources of exposure, the RR using the most wide-ranging definition will be included; it follows that the "most" non-exposed comparison group will almost certainly be the only one available. Therefore when a variant meta-analysis is run by choosing the "least unexposed" comparison group, this is likely to choose exactly the same RRs. On the other hand, if the key meta-analysis refers to maternal smoking and "most" non-exposure, then it is much more likely that, within some studies, there will be a choice of RRs with different comparison groups (e.g. mother does not smoke, neither parent smokes, no smoker in household); thus the variant meta-analysis with "least unexposed" comparison group is likely to have a larger number of studies where a different RR is included when compared with the key meta-analysis.

7.10.6. Factors Considered

Meta-analyses were carried out both overall, for all the RRs selected, and then by the factor *sex*, with estimates compared, for combined-sex results and those specifically for males and females. Depending on the particular exposure being considered, further analyses may use some of the following factors/levels:

Asthma: Lifetime; current.

Continent: NAmer (North America); SCAmer (South or Central America); Europe; Asia; Auslia (Australasia); Africa *for children.*
NAmer; Europe; Oth/Mult (Other/Multiple) *for adults.*

Country in Europe: UK; Italy; Germany; Scand (Scandinavia); othWest (other West European countries: France, Ireland, Netherlands, Spain and Switzerland); East/Bal (East European and Balkan countries: Poland, Russia and Turkey).

Country in Asia: Far East (China, Japan, Hong Kong, Taiwan and Korea); Cent/SE (Central and SE: Malaysia, India, Nepal and Sri Lanka); MidlEast (Middle East: Israel, Saudi Arabia and UAE).

Start year of study: <1970; 1970-79; 1980-89;1990+; unknown *for children*.
<1990; 1990-99; unknown *for adults.*

Publication year: <1990; 1990-94; 1995-99; 2000+ *for children*.

1990-1999; 2000+ *for adults.*

This refers to the principal publication for the study.

Study type: CC (Case-control); Pr (Prospective); CS (Cross-sectional). (See also §9.1.4 for children.)

Ex-smokers: excluded; included.

This refers to how active smoking by the (adult) subject was treated.

Highest age in RR: 0-9; 10-14; 15+; unknown *for children.*

Up to 55; 60-69; 70+ *for adults*.

Lowest age in RR: 15-19; 20-25; 60+ *for adults.*

Population / setting: general (studies covering all children or randomly selected children in an area, or household surveys); school (studies of school pupils); medical (studies carried out in a medical setting, including school health checks, and new-borns recruited at maternity facilities); allergy (studies of children with a family history of asthma or allergic conditions); other (school athletes, children living on farms, twins, travellers, children at high risk of SIDS, and unspecified).

Respondent for ETS exposure/maternal smoking in pregnancy: child (questionnaire completed by the child); parent (questionnaire completed by a parent); med rec (data extracted from medical records); mix/oth (a mixture of sources, or other household member).

Child smokers: exc/none (those studies where smokers were specifically excluded from analysis, having been identified either biochemically or by questionnaire, those studies which looked for smokers but found there were none, and those studies which explicitly assumed there were no smokers due to the young age of the subjects); included (those studies where smokers were known to exist and were included in analysis, including studies which adjusted for, or tested for, effects of child's smoking in the analysis); ignored (studies which did not mention the possibility of smoking by the children, often because they were conducted in young children, and those studies which mentioned the possibility but took no action), *for children.*

This refers to how the study treated smoking by the child in its analysis.

Physician diagnosis: yes (diagnosis by physician); no/mixed (self-diagnosis, definition based on a list of reported symptoms, or physician diagnosis plus self-report of symptoms).

Respondent for diagnosis: medrec (diagnosis extracted from medical records or made by the physician conducting the survey); parent (from a questionnaire completed by the parent); child (from a questionnaire completed by the child); mixed (a mixture of sources or unspecified).

Questionnaire for symptoms: ISAAC (International Study of Asthma and Allergies in Childhood); ATS (American Thoracic Society); other.

Analysis type: prevlence (prevalence); onset.

Number of cases: 1-50; 51-100; 101-200; 201+; unknown *for children.*

1-100; 101-400;401+; unknown *for adults.*

This refers to the number of asthma cases (lifetime or current as relevant to the meta-analysis) in the whole study, rather than in the specific RR.

Study adjustment: Yes; no.

A number of factors refer to whether any of the RRs on the data base were adjusted for certain potential confounders, although the specific RR included in a meta-

analysis may not have been adjusted for that confounder. The confounders considered (which vary somewhat for children and adults) include: sex; age; race; location; SES (socio-economic status); family medical history; family composition (e.g. number of siblings, single parent); cooking, heating or air conditioning (including type of fuel, use of dehumidifiers or mosquito coils); housing quality, crowding, damp, mould; pets, animal contact or farming; medical history (including breastfeeding, nutrition and allergy skin prick tests); ETS exposure *in utero*; ETS exposure in lifetime; ex-smoking. Matching in the study design (for case-control studies only) was considered equivalent to adjustment for confounding where appropriate.

Source of ETS exposure: Biochem (biochemically assessed exposure); TotETS (questionnaire-based total ETS exposure); AnyHh (exposure from any household member); AnyPar (exposure from mother and/or father); Mother (exposure from mother irrespective of father); MothOnly (exposure from the mother but not the father); Father; FathOnly; Other; OthrOnly (defined similarly to Mother and MothOnly but relating to the father or to household members other than the parents); Grandpar (exposure from grandparents or grandfather); Sibling (exposure from siblings) *for children.*

Hh (household); Hh,Wk (household and/or workplace); Cot (serum cotinine); Work *for adults.*

The levels included depend on the specific meta-analysis.

Timing of exposure: lif/ev (exposure in child's life, ever in smoker's life, or in-life and/or *in utero*); age<7y (at a specific age which is wholly below age 7); current; unspec (unspecified); other (other specific ages or not applicable, e.g. for biochemically assessed exposure) *for children.*

Life (any in subject's lifetime); adult (in adulthood or in last 6 homes); child (in childhood); current; unspec (unspecified) *for adults.*

Discontinued exposure: Ex (ever in smoker's life but not current); LifeNotC (exposure in life but not current).

Unexposed group: who is smoker: NoHhMemb (no household member smokes); NoParent (neither parent smokes); NotSpPar (specified parent does not smoke); NotSpHhM (specified household member does not smoke).

Unexposed group: time: non (not at the time specified by time of exposure); never (never smoked in smoker's life); non+other (not at the time specified by time of exposure and not at some additional time); NA (not applicable i.e. for biochemical exposure).

Measure of exposure: cigs (number of cigarettes exposed to or smoked by smoker); persn (number of persons smoking in household); other (minutes per day or occasional/several hours per day).

Number of adjustment variables: 0; 1; 2; 3-5; 6-9; 10+.

This refers to the adjustment variables used in the specific RR included in the meta-analysis.

Relative risk adjustment: yes; no.

This refers to the adjustment variables used in the specific RR included in the meta-analysis, rather than in the study as a whole, as above. The variables considered include: sex; age; ex-smoking; other ETS (i.e. other than the specific exposure to which the RR refers); any other variables.

Derivation of RR/CI: Original; Numbers (calculated from the 2×2 table, adjusted calculation from a 2×2×n table, or recalculation due to a discrepancy between a 2×2 table and an original RR/CI); SumNumbs (calculation from 2×2 table after combining categories); other (other methods, as described in §7.9).

7.10.7. Meta-analysis of Results by Amount of Exposure

Results by amount of exposure generally take the form of a RR for each of a set of categories (e.g. mother smokes 1-10, 11-20 etc cigarettes) compared with a common base group, e.g. mother non-smoker. These are not independent.

The approach adopted is to use only the first and last from each set of categories, then to carry out a standard meta-analysis for each level. Effectively only one RR is chosen from each study for each level, thus ensuring independent results for a valid meta-analysis of "low dose" and "high dose" respectively. The sets of categories are included irrespective of the measure of exposure used, and for those studies which give results for more than one measure, they are chosen in the following order of preference: biochemical measures; number of cigarettes; number of persons smoking[5]; time per day of exposure. Because the individual studies used different definitions for the categories, the range of values included in the "low" and "high" analyses may overlap. For instance, if one study used the categories 1-10 and 11+, while another used 1-29 and 30+, then exposure to 11-29 cigarettes would be included in the low category for one study, but in the high category for the other. However this approach ensures that the same studies are included in both of the low/high pair of analyses, and allows within-study comparisons to be made. Relatively few of the sets contained three or more categories, so it was not practical to carry out any meta-analysis of "medium dose."

For selected meta-analyses by amount of exposure a forest plot is shown. The layout is as described at the end of §7.10.3, differing only in that the plot shows low dose results in the upper half of the plot, with high dose results in the lower half.

7.10.8. Meta-analysis of Results by Age

Meta-analysis by age was only conducted for children. Two approaches were adopted. Firstly, the main meta-analyses, based on results for the whole study or the widest available age range for the exposure of interest, use age as a factor.

The second approach is to define a set of age groups, and to carry out standard meta-analyses of the RRs relevant to each age group separately. Although this is to some extent similar to the approach taken for results by amount of exposure, a fundamental difference is that results for different age groups are independent, and there is therefore no constraint to choose just one result per study for each analysis. RRs are only accepted for age ranges that fall completely within the age range specified. These may be either age-specific results from studies with a wide age range, or whole-study results from studies with narrow age criteria. The age groups considered are <10; including 10; and >10 years.

[5] Results for the number of parents who smoke (i.e. none, one only, both) have not been analysed as dose-response – see chapter 9.

7.10.9. Presentation of Findings in Chapters 8 and 9

In most of the text of this report we refer to the output as being in e.g. Table C6 even where, in the case of meta-analyses which are not selected as "key," results can only be found in Appendix Table C6, available at *www.pnlee.co.uk/etsast.htm.*

RRs and 95% CIs are typically referred to simply as e.g. 1.23 (1.18-1.28), where it is obvious in the text that these are what are referred to. The standard notation may be extended to e.g. 1.23 (1.18-1.28, n=32) or 1.17 (1.10-1.25, $p<0.001$) to indicate the number of RR estimates on which a meta-analysis estimate is based or the level of significance. Unless otherwise stated, it should be assumed that meta-analysis RR estimates cited are fixed effects, and that they are calculated using individual estimates that are adjusted for covariates where there is a choice of unadjusted and adjusted estimates.

7.11. REFERENCES

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Chapter 8

INDUCTION OF ASTHMA – EVIDENCE IN NON-SMOKING ADULTS

8.1. THE STUDIES

8.1.1. Studies Identified

Based on the methods described in §7.1, a total of 460 papers were identified, of which 454 could be obtained and examined. Of these, 28 contained relevant data and 15 were review papers, with the remaining 411 providing no relevant data at all. The 28 papers related to 17 studies.

Table 8.1 gives certain details of the 17 studies; the 6-character reference used to identify the study, a longer study title (which includes information on the location and timing of the study), and the references to the principal publication used to extract the data and to any other relevant publications.

8.1.2. The Study Data

The computer-generated report giving the data recorded on the study database for each of the 17 studies is available from *www.pnlee.co.uk/etsast.htm* [Appendix 11].

8.1.3. Overlapping Studies

As discussed in §7.6, there are potential problems with overlapping studies. For adults, however, only one pair of overlapping studies was identified. Results for current asthma from the multicentre European Community Respiratory Health Study (ECRHS) were entered as study JANSON and marked as a principal study. In addition, results for lifetime asthma from one of the centres (Bordeaux) were also entered as study RAHERI, and marked as the subsidiary study.

(It should also be noted that results from the adult study NHANE3 are for age 17+ and do not overlap with the childhood results for ages 0-16 considered in chapter 9. There is no overlap between the adult and childhood data.)

Table 8.1. The 17 studies considered – non-smoking adults

Study Ref	Study title	Principal publication	Additional publication(s)
BECKE2	CARDIA[1] 4 city PS 1985-1996	Beckett et al., 2001	Friedman et al., 1988
JAAKK3	Pirkanmaa incident asthma CC 1997-2000	Jaakkola et al., 2003	-
JANSON	ECRHS[2] multicentre CS 1990-94	Janson et al., 2001	Svanes et al., 2004; de Marco et al., 2004
JEDRYC	Cracow elderly TB screening CS (ca 1994?)	Jedrychowski et al., 1995	-
KRONQV	Gotland farmers CS 1996	Kronqvist et al., 1999	-
LARSS1	Swedish part of FinEsS[3], Orebro CS 1995-6	Larsson et al., 2001	-
LARSS2	Estonian part of FinEsS[3], 3 centre CS 1995	Larsson et al., 2003	-
MISHRA	Indian NFHS-2[4] elderly CS 1998-99	Mishra, 2003	-
NG	Singapore CS (ca 1992?)	Ng et al., 1993	-
NHANE3	NHANES III[5] nationwide CS 1988-94	Eisner, 2002b	-
ORYSZC	French EGEA[6] CC (ca 1996?)	Oryszczyn et al., 2000	Kauffmann et al., 1997
PILOTT	Port Adelaide CS 1995	Pilotto et al., 1999	-
PLATTS	Wilmington acute asthma CC 1988-89	Platts-Mills & Call, 1993	Moyer, 1993; Gelber et al., 1993
RAHERI	ECRHS[2] Bordeaux centre CS 1991-92	Raherison et al., 2003	-
ROBBIN	California 7th Day Adventist PS 1977-87	Robbins et al., 1993	Greer et al., 1993; McDonnell et al., 1999
SAPALD	SAPALDIA[7] CS 1991	Leuenberger et al., 1994	Leuenberger et al., 1993; Zemp et al., 1999; Künzli et al., 2000
THORN	Alvsborg nested CC 1994	Thorn et al., 2001	-

CC = case-control study; CS = cross-sectional study; PS = prospective study.

[1] CARDIA = Coronary Artery Risk Development in Young Adults.

[2] ECRHS = European Community Respiratory Health Study.

[3] FinEsS = epidemiologic studies in Finland, Estonia and Sweden.

[4] NFHS-2 = 2nd National Family Health Survey.

[5] NHANES III = Third National Health and Nutrition Examination Survey.

[6] EGEA = Epidemiological Study of the Genetics and Environment of Asthma.

[7] SAPALDIA = Swiss Study on Air Pollution and Lung Diseases in Adults.

8.1.4. Study Characteristics

Table 8.2 gives the distribution of various selected study characteristics by study type and overall. Except where specified otherwise, the discussion in the rest of this section refers to the principal studies only.

Table 8.2. Characteristics of the 17 studies – non-smoking adults

Characteristic : Level		Number of studies by study type[1]				
		CC	Prosp	CrSec	Subsid	Total
Total		4	2	10	1	17
Study sex :	both	4	2	8	1	15
	female	0	0	2	0	2
Lowest age in study :						
	15	1	0	3	0	4
	17	0	0	1	0	1
	18	0	1	2	0	3
	20	1	0	2	1	4
	21	1	0	0	0	1
	25	1	1	0	0	2
	60	0	0	1	0	1
	65	0	0	1	0	1
Highest age in study (for prospective studies refers to baseline) :						
	30	0	1	0	0	1
	44	0	0	0	1	1
	48	0	0	1	0	1
	50	1	0	0	0	1
	54	1	0	0	0	1
	55	1	0	0	0	1
	60	0	0	1	0	1
	63	1	0	0	0	1
	64	0	0	1	0	1
	65	0	0	1	0	1
	69	0	0	1	0	1
	74	0	0	1	0	1
	no upper limit	0	1	4	0	5
Highest age in study at final follow-up :						
	40	-	1	-	-	1
	no upper limit	-	1	-	-	1
Study race :	all (in country)	4	0	10	1	15
	whites and blacks	0	1	0	0	1
	non-Hispanic whites	0	1	0	0	1
Continent :	N America	1	2	1	0	4
	Europe	3	0	5	1	9
	Asia	0	0	2	0	2
	Australia	0	0	1	0	1
	multi	0	0	1	0	1

Table 8.2. Continued

Characteristic : Level		Number of studies by study type[1]				
		CC	Prosp	CrSec	Subsid	Total
US state :	all	0	0	1	0	1
	multi	0	1	0	0	1
	California	0	1	0	0	1
	Delaware	1	0	0	0	1
Country :	Estonia	0	0	1	0	1
	Finland	1	0	0	0	1
	France	1	0	0	1	2
	Poland	0	0	1	0	1
	Sweden	1	0	2	0	3
	Switzerland	0	0	1	0	1
	India	0	0	1	0	1
	Singapore	0	0	1	0	1
Start year of study :						
	1970-1979	0	1	0	0	1
	1980-1989	1	1	1	0	3
	1990-1999	2	0	7	1	10
	missing	1	0	2	0	3
End year of study (for prospective studies refers to baseline) :						
	1970-1979	0	1	0	0	1
	1980-1989	1	1	0	0	2
	1990-1999	1	0	8	1	10
	2000	1	0	0	0	1
	missing	1	0	2	0	3
Final follow up year :						
	1990-1999	-	2	-	-	2
Principal publication year :						
	1990-1999	1	1	5	0	7
	2000-2003	3	1	5	1	10
Type of population[2] (for CC studies refers to cases) :						
	all	2	0	1	0	3
	randomly selected	1	2	6	1	10
	farmers	0	0	1	0	1
	random households	0	0	2	0	2
	unstated	1	0	0	0	1
Type of controls :						
	healthy	2	-	-	1	3
	diseased/hospital	1	-	-	0	1
	both	1	-	-	0	1
Type of control population :						
	same as cases	4	-	-	0	4
	without history of asthma	0	-	-	1	1
Matched on sex		1	-	-	0	1
Matched on age		1	-	-	0	1
Respondent (for ETS exposure information) :						

Table 8.2. Continued

Characteristic : Level	Number of studies by study type[1]				
	CC	Prosp	CrSec	Subsid	Total
subject	4	2	9	1	16
head of household	0	0	1	0	1
Lifetime[3]/incidence asthma available	1	2	5	1	9
Source of lifetime[3]/ incidence asthma diagnosis :					
medical records	0	0	1	0	1
self report (physician diag)	1	1	3	1	6
self report (other/unspecified/ mixed)	0	1	1	0	2
Timing of lifetime[3] asthma :					
lifetime	0	1	1	1	3
unspecified	0	0	4	0	4
from age 16	1	0	0	0	1
NA (incidence only)	0	1	0	0	1
Timing of incidence asthma :					
since baseline (earlier excl)	0	2	0	0	2
NA (prevalence only)	1	0	5	1	7
Number of lifetime[3]/ incidence asthma cases :					
1-100	1	1	0	1	3
101-200	0	0	1	0	1
201-500	0	1	1	0	2
median	69	276.5	215	96	119.5
min	69	8	143	96	69
max	69	473	287	96	473
missing	0	0	3	0	3
Current asthma available	3	0	6	0	9
Current asthma is first occurrence	1	0	0	0	1
Repeat measures for current asthma	-	0	-	-	0
Source of current asthma diagnosis :					
Medical records	2	0	0	0	2
Self report (physician diag)	0	0	3	0	3
Self report (other/unspec/mixed)	1	0	2	0	3
Proxy report (other/unspecified/ mixed)	0	0	1	0	1
Timing of current asthma :					
current diagnosis	2	0	1	0	3
last 12 months	1	0	3	0	4
current NOS	0	0	2	0	2
Number of current asthma cases :					
1-100	2	0	2	0	4
101-200	0	0	0	0	0
201-500	1	0	1	0	2
501-1000	0	0	0	0	0
>1000	0	0	1	0	1
median	51	-	269.5	-	99

Table 8.2. Continued

Characteristic : Level	Number of studies by study type[1]				
	CC	Prosp	CrSec	Subsid	Total
min	48	-	33	-	33
max	239	-	2479	-	2479
missing	0	0	2	0	2
Total number of subjects :					
1-100	1	0	0	0	1
101-200	1	0	0	0	1
201-500	1	0	0	0	1
501-1000	1	0	1	1	3
1001-5000	0	2	5	0	7
>5000	0	0	4	0	4
median	313	3365	3490.5	544	1282
min	89	3128	581	544	89
max	726	3602	28020	544	28020
missing	0	0	0	0	0
Other definitions of asthma available	0	1	3	0	4
Wheezing/wheezing bronchitis available	0	0	6	1	7
Other exposures available	0	0	1	0	1
Non-smoker definition :					
never smoked NOS	2	0	2	0	4
smoked <1 cig/day for 1 year	0	0	2	0	2
never smoked, not even a few per week	0	0	1	0	1
never smoked regularly/daily	1	0	1	0	2
smoked <20 packs cigarettes or 360g tobacco in lifetime	0	0	1	0	1
smoked <1 cigarette/day or 1 cigar/week for a year, or 360g tobacco in lifetime	0	0	1	0	1
smoked for <1 year	0	0	0	1	1
not current smoker	0	1	1	0	2
not active smoker	1	0	0	0	1
serum cotinine <14 ng/ml	0	0	1	0	1
not current smoker and serum cotinine <14 ng/ml	0	1	0	0	1
Results for other definition of non-smokers available	0	0	3	1	4
Total number of adjustment factors used :					
none	2	0	1	0	3
2	1	0	0	0	1
3	0	0	3	0	3
4-5	0	1	1	0	2
6-8	0	1	3	0	4
10-15	1	0	2	1	4

Table 8.2. Continued

Characteristic : Level	Number of studies by study type[1]				
	CC	Prosp	CrSec	Subsid	Total
Confounders considered[4]					
- sex	1	2	6	1	10
- age	2	2	9	1	14
- race	0	1	1	0	2
- location (includes urban/rural, air pollution)	0	2	6	0	8
- family medical history	1	0	2	1	4
- SES	0	0	1	0	1
- household composition	0	0	2	0	2
- cooking	0	0	3	0	3
- mould in home or workplace	1	0	0	0	1
- housing quality	0	0	2	0	2
- pets	1	0	0	0	1
- exposure to allergens	0	0	1	0	1
- occupation	1	0	3	0	4
- religion	0	0	1	0	1
- education	1	2	2	0	5
- personal medical history :					
(by 1-3 variables)	1	1	1	0	3
(by > 3 variables)	0	0	1	1	2
- body mass index	0	0	2	0	2
- active smoking (never/ex)	0	1	0	0	1
- childhood ETS	0	0	1	0	1
- total (adult) ETS	0	0	1	0	1
- household ETS exposure	1	0	2	0	3
- workplace ETS	1	1	2	0	4
Other confounders considered but rejected	0	1	1	0	2
Results by other stratifying factors available	0	0	3	0	3

[1] CC = case-control; Prosp = prospective; CrSec = Cross-sectional; Subsid = Subsidiary.

[2] Refers to persons within the study area, age group etc as defined by other variables.

[3] Includes asthma of unspecified timing.

[4] By up to three variables, unless stated otherwise.

Design. Of the 16 principal studies, four are case-control, two prospective, and 10 of cross-sectional design. The case-control studies varied in their method of identifying cases. In THORN, and also in the subsidiary study RAHERI, an initial cross-sectional phase was carried out to identify cases. In study JAAKK3, all new asthma cases were identified through all health care facilities in the region supplemented by checks of the National Social Insurance Institution computerized records. The remaining two case-control studies recruited patients at a chest clinic (ORYSZC) and at a hospital emergency department (PLATTS).

Sexes considered. All studies included both sexes, except for two which considered females only (JEDRYC in Poland and NG in Singapore).

Age of subjects. The lower age limit was in the range 15-25 in all but two studies – JEDRYC in Poland (65) and MISHRA in India (60). For the case-control studies, the upper

age limit was between 50 and 63, while for the cross-sectional studies it was above 60 with one exception (JANSON multicentre study - 48). In the two prospective studies, the age at baseline was 18-30 for BECKE2 and 25+ for ROBBIN.

Race of subjects. In 14 studies, there was no selection on race though clearly variation in the location of the study would cause major variation in the racial distribution. The two studies restricted on race were both conducted in USA – BECKE2 restricted to whites and blacks, and ROBBIN restricted to non-Hispanic whites.

Location. Studies were most commonly conducted in Europe (8: three in Sweden and one each in Estonia, Finland, France, Poland and Switzerland) or USA (4: one nationwide, one multi-state and one each in California and Delaware), with two studies in Asia (India and Singapore), one in Australia, and one multi-country study (USA, Australia, New Zealand and 14 European countries).

Timing. The timing of the study was not stated for three studies. The two prospective studies were the earliest, starting in 1977 – ROBBIN and 1985 – BECKE2, respectively. All other studies started between 1988 and 1998. For all of the studies, the principal publication year was 1993 or later.

Population studied. Most studies were of the general population with no major restrictions, two exceptions being KRONQV – farmers and ROBBIN – Seventh Day Adventists. Some studies imposed further restrictions, as detailed in *www.pnlee.co.uk/ etsast.htm* [Appendix 12.1]. Although these were generally of a minor nature, some may have materially affected the representativeness of the population studied. For instance JEDRYC excluded *"residents of old-people's homes or long-stay geriatric wards, who are more likely to have more respiratory problems and poorer lung function."* One study gave no information about the population considered.

Although no information has been entered on the database regarding response or retention rates, it can be noted that the two prospective studies based their analysis on subjects who were alive and could be traced for at least one follow-up. One of them (ROBBIN) further restricted attention to subjects who had lived within 5 miles of their baseline address for at least 10 years, and the cross-sectional study SAPALD restricted analysis to subjects who had lived in the region for 3 years. Thus they may have under-represented subjects from more mobile families.

Type of controls. Among the case-control studies, three used healthy (population) controls – JAAKK3, THORN and subsidiary study RAHERI. PLATTS used patients presenting at the same hospital emergency department with any condition other than breathlessness. ORYSCZ used mainly population controls, but also some recruited through surgery departments and from a check-up centre.

Matching factors. In study PLATTS, the cases and controls were matched on sex and age. There were conflicting reports as to whether study ORYSZC was matched (unmatched according to Oryszczyn et al. [2000] but matched on age, month and centre according to Kauffmann et al. [1997]), while the other case-control studies were unmatched.

Respondent. In all studies information about the passive smoke exposure was provided by the subject, with the exception of MISHRA where the head of household responded on behalf of all household members.

Definition of disease outcome – lifetime and incident asthma. Results for lifetime or incident asthma (including prevalent asthma of unspecified timing) were available from eight

principal studies (one case-control, five cross-sectional and the two prospective studies), and also from subsidiary study RAHERI.

In all but one study, the asthma diagnosis had been made by a doctor, this diagnosis being made in a medical examination as part of the study design in study KRONQV, otherwise as reported by the subject; the exception was study PILOTT which used self-reported asthma. Study ROBBIN presented results for two different definitions of asthma, with one paper (McDonnell et al., 1999) using "physician-diagnosed asthma" (in relation to household or workplace ETS exposure), and another (Robbins et al., 1993) using "physician-diagnosed asthma with a history of wheezing" (in relation to total ETS exposure).

Both the prospective studies presented results for onset during the study (i.e. excluding subjects with pre-existing asthma at baseline), with BECKE2 also presenting results for baseline prevalence of asthma. In study THORN, only adult-onset asthma was included (onset after age 16 and not more than 15 years ago, the subjects being age 20-50 at the time of the study). Further details of the asthma definition are available from *www.pnlee.co.uk/etsast.htm* [Appendix 12.2].

Definition of disease outcome – current asthma. Results for current (i.e. active) asthma were available from 9 studies, three case-control studies, and six cross-sectional. In one of the case-control studies (JAAKK3), this was restricted to being the first episode of asthma, with the cases identified at all health care facilities in the region or through computerized records of prescriptions for asthma medications. In study PLATTS cases were recruited when presenting at a hospital emergency department with acute asthma, in study ORYSZC they were attending a chest clinic.

An asthma diagnosis was made by a physician (either as reported by the subject or in the course of the study design), usually with the subject also reporting symptoms or treatment, currently or in the last 12 months; exceptions were studies JANSON and MISHRA which used self- (or proxy-) reported asthma. Further details are again available from *www.pnlee.co.uk/etsast.htm* [Appendix 12.2].

Only study SAPALD, and the overlapping pair of studies JANSON/RAHERI, presented results for both lifetime and current asthma.

Availability of alternative disease outcome. For four studies results were available for alternative asthma definitions; these results have not been entered on the database. See *www.pnlee.co.uk/etsast.htm* [Appendix 12.3] for further details. The availability of results for wheeze was also noted for six studies.

Study size. Where the number of cases was known, for lifetime or incident asthma, it ranged from 69 to 473, with the median being 119. The largest was BECKE2 (with 473 combined baseline and onset cases). For current asthma, the range was 33 to 2479, with median 99. By far the largest study was MISHRA, conducted in India with 2479 current asthma cases, followed by NHANE3 in USA with 440. In addition, there were three other large studies (>1000 subjects) for which the number of asthma cases was not given.

Exposures. For the exposure types entered on the database (§7.8.2) information is presented in §8.2. Only study NHANE3 provided information on any other aspect of ETS exposure. In this study, median serum cotinine was also available in subjects with and without asthma.

Definition of non-smoking, In 11 principal studies, the results referred to self-reported never smokers, or to those whose lifetime smoking history was less than some defined amount. These included three case-control studies (and also the subsidiary study RAHERI),

and eight cross-sectional studies. The other studies refer to non-smokers (i.e. not currently smoking), based on self-report (PILOTT, PLATTS, ROBBIN), biochemical assessment (BECKE2) or both (NHANE3). In the prospective studies, assessment was made at baseline in study BECKE2, while in ROBBIN, subjects are all members of the Seventh Day Adventist Church which does not permit smoking (although some subjects may have smoked before joining the church).

Alternative results which have not been entered on the database are available for some studies. Two of the studies providing data for never smokers (JANSON, KRONQV) also presented results for ex-smokers, while SAPALD had results for never smokers validated biochemically. RAHERI also had results for ever smokers restricted to asthma onset before starting to smoke.

Confounders. Three studies did not adjust for any variable at all in analysis, although one of these (PLATTS) was matched on sex and age. About half of the studies adjusted for four or more potential confounders, with three adjusting for 10 or more.

Table 8.2 also shows all those variables taken account of. Age and sex are the commonest, with 13 and 9 studies adjusting for them respectively. Other more commonly used variables were location (8 studies), education (5), occupation (4), aspects of personal (4) or family (3) medical history, cooking methods (3), and housing quality, crowding or mould (3).

Never/ex- smoking was used as an adjusting factor in one of the studies of non-smokers (ROBBIN). Results adjusted for other aspects of passive smoking were available for four studies. No study adjusted for maternal smoking in pregnancy, although study SAPALD presented results excluding subjects whose mothers had ever smoked (not entered on database).

Additional confounders were formally considered by the study authors but rejected from analysis in a stepwise multiple logistic regression in two studies (KRONQV, ROBBIN).

Other stratifying variables. Only sex, age and race were considered as stratifying variables in the RR database, and in practice, no results stratified by age, race or by any other stratifying variables were found. Details of which studies presented results for particular subsets of the subjects are available from *www.pnlee.co.uk/etsast.htm* [Appendix 12.4].

8.2. THE RELATIVE RISKS

Based on the methods described in §7.8 and §7.9, a total of 117 RRs were entered on the database, of which 115 relate to the principal studies and two to the subsidiary study. Among the 16 principal studies, 10 have between one and four RRs, and a further five have between 5 and 14 RRs, while study JAAKK3 has 48 RRs (Table 8.3).

Table 8.4 gives the distribution of various selected RR characteristics by study type and overall, based on all the 17 studies. Table 8.5 shows how many of the principal studies or their subsidiary had RRs with selected characteristics, and except where specified otherwise, in the discussion in the rest of this section “study” refers to “a principal study or its subsidiary.”

Table 8.3. Relative risks available per study – non-smoking adults

Study Type	Study Ref	Number of RRs by exposure type			
		Total ETS	Household	Workplace	Total
Case-control	JAAKK3	16	16	16	48
	ORYSZC	0	2	2	4
	PLATTS	1	0	0	1
	RAHERI[1]	2	0	0	2
	THORN	0	3	0	3
Prospective	BECKE2	4	0	0	4
	ROBBIN	10	2	2	14
Cross-sectional	JANSON	4	5	1	10
	JEDRYC	0	1	0	1
	KRONQV	1	1	1	3
	LARSS1	0	2	0	2
	LARSS2	0	1	4	5
	MISHRA	0	4	0	4
	NG	0	6	0	6
	NHANE3	0	1	1	2
	PILOTT	0	1	0	1
	SAPALD	6	0	1	7

[1] subsidiary study.

Table 8.4. Characteristics of the 117 relative risks – non-smoking adults

Characteristic : Level		Number of RRs by study type[1]				
		CC	Prosp	CrSec	Subsid	Total
Total		56	18	41	2	117
Sex :	both	50	14	26	2	92
	male	3	2	4	0	9
	female	3	2	11	0	16
Time of asthma :	lifetime	3	18	17	2	40
	current	53	0	24	0	77
Onset :	no	56	2	41	2	101
	yes	0	16	0	0	16
Odds ratio (onset analysis)		-	14	-	-	14
Exposure type :	household	21	2	22	0	45
	workplace	18	2	8	0	28
	total	17	14	11	2	44
Household exposure – who smoked :						
	all	21	2	18	0	41
	mother	0	0	2	0	2
	father	0	0	2	0	2
Total exposure – source :						
	total NOS	1	0	1	2	4
	home and/or work	16	10	10	0	36
	serum cotinine	0	4	0	0	4

Table 8.4. (continued)

Characteristic : Level		Number of RRs by study type[1]				
		CC	Prosp	CrSec	Subsid	Total
Time of exposure :						
	lifetime	30	5	6	0	41
	current	22	4	27	0	53
	childhood/youth	0	2	7	1	10
	adult	0	2	0	0	2
	recent years	3	0	0	0	3
	unspecified	1	0	1	1	3
	childhood (not adult)	0	2	0	0	2
	adult (not childhood)	0	2	0	0	2
	both adult and child	0	1	0	0	1
Dose-response :	all (not dose-response)	20	14	28	2	64
	level 1	12	0	4	0	16
	level 2	12	0	4	0	16
	level 3	6	0	2	0	8
	level 4	6	0	0	0	6
	per unit dose regression	0	4	0	0	4
	other	0	0	3	0	3
Measure of exposure :						
	yes/no	20	10	28	2	60
	cigarettes/day	12	0	4	0	16
	years	0	4	1	0	5
	pack-years	24	0	0	0	24
	hours/day	0	0	7	0	7
	persons	0	0	1	0	1
	ng/ml	0	4	0	0	4
Unexposed – time :						
	non	56	13	41	2	112
	never	0	5	0	0	5
Unexposed – source :						
	none (or low)	17	14	12	2	45
	none of type (as in *Exposure type*)	39	4	25	0	68
	not specified household member	0	0	4	0	4
N adjusted for :	0	30	2	9	1	42
	2	2	0	0	0	2
	3	0	0	3	0	3
	4-5	0	16	8	0	24
	6-8	24	0	13	0	37
	9-12	0	0	8	1	9
Adjusted for						
- sex		24	12	22	1	59

Table 8.4. (continued)

Characteristic : Level		Number of RRs by study type[1]				
		CC	Prosp	CrSec	Subsid	Total
Adjusted for						
- age		26	16	32	1	75
- race		0	2	3	0	5
- active smoking (never/ex)		0	12	0	0	12
- other sources of ETS :						
	none	40	17	26	2	85
	1	16	1	13	0	30
	2	0	0	2	0	2
- other confounders :						
	none	30	2	9	1	42
	1	2	0	2	0	4
	2	0	12	9	0	21
	3	0	4	0	0	4
	4	0	0	7	0	7
	5	24	0	0	0	24
	6	0	0	12	0	12
	8	0	0	0	1	1
	11	0	0	2	0	2
Unadjusted RRs						
- numbers of cases available		29	2	9	1	41
- numbers of controls/at risk available		29	2	9	0	40
- full 2 × 2 table available		29	2	9	0	40
Adjusted RRs - numbers of cases available		24	2	10	0	36
RR :	0.01-1.00	16	6	11	1	34
	1.01-2.00	27	8	22	1	58
	2.01-4.00	10	0	0	0	10
	4.01+	2	0	0	0	2
	median	1.52	1.49	1.15	0.96	1.32
	min	0.43	0.66	0.53	0.30	0.30
	max	4.80	1.89	1.90	1.62	4.80
	missing	1	4	8	0	13
CI available :	no	1	4	8	0	13
	yes	55	14	33	2	104
Derivation of RR/CI :						
	original	23	5	22	2	52
	RR/CI from numbers	24	2	8	0	34
	RR/CI recalculated from numbers	2	0	0	0	2
	sum over exposure levels	3	0	1	0	4
	non-significant	1	3	5	0	9
	significant	0	1	3	0	4
	F&L[2] over exposure levels	3	7	2	0	12

[1] CC = case-control; Prosp = prospective; CrSec = Cross-sectional; Subsid = Subsidiary.
[2] F&L = method of Fry and Lee (2000).

Table 8.5. Relative risk characteristics available from the 16 principal studies (or their subsidiary) – non-smoking adults

Characteristic	Number of studies[1] by study type[2]			
	CC	Prosp	CrSec	Total
Total	4	2	10	16
Single sex	2	1	4	7
Lifetime or incidence asthma	1	2	6	9
Current asthma	3	-	6	9
Onset analysis	-	2	-	2
Odds ratio for onset analysis	-	1	-	1
Exposure type :				
household	3	1	9	13
workplace	2	1	5	8
total	2	2	3	7
Household exposure – who smoked :				
all	3	1	9	13
mother	0	0	1	1
father	0	0	1	1
Total exposure – source :				
all	1	0	2	3
home and/or work	1	1	2	4
serum cotinine	0	1	0	1
Time of exposure :				
lifetime	1	1	1	3
current	2	1	7	10
adulthood	0	1	0	1
childhood	0	1	3	4
recent years	1	0	0	1
unspecified	1	0	2	3
joint exposures Adult × Child	0	1	0	1
Dose-response data	1	0	3	4
Measure of exposure :				
yes/no	4	1	10	15
cigarettes/day	1	0	1	2
years	0	1	1	2
pack-years	1	0	0	1
hours/day	0	0	3	3
persons	0	0	1	1
ng/ml	0	1	0	1
Unexposed – time				
non	4	2	10	16
never	0	1	0	1
Unexposed – source:				
none (or low)	2	2	3	7
none of type	3	1	9	13
not specific household member	0	0	1	1

Table 8.5. (continued)

Characteristic	Number of studies[1] by study type[2]			
	CC	Prosp	CrSec	Total
Adjustment for				
- sex	1	2	6	9
- age	2	2	9	13
- race	0	1	1	2
- active smoking (never/ex)	0	1	0	0
- other ETS exposure	1	1	2	4
- other non-ETS variables	2	2	9	13
- any adjustment	2	2	9	13
- no adjustment	4	1	6	11
Number of cases available	3	1	6	10
RR available	3	2	9	14
CI available	3	2	9	14
Derivation of RR/CI :				
original	2	2	8	12
from numbers	3	1	5	9
recalculated	1	0	0	1
summed levels	1	0	1	2
significant/non-significant	1	1	3	5
F&L[3]	1	1	2	4

[1] Number of principal studies which have (or which have a subsidiary study which has) at least one RR with the characteristic.

[2] CC = case-control; Prosp = prospective; CrSec = Cross-sectional.

[3] Method of Fry and Lee (2000).

Sex. Only five studies gave any results for males and females separately, in addition to the two studies which included females only. The great majority of RRs (92, 79%) are for sexes combined.

Asthma type. The RRs are predominantly for current (77) asthma prevalence, particularly from the case-control studies (53 RRs, 95%). 24 of the rest refer to lifetime prevalence and 16 refer to incidence, with 14 of these actually being odds ratios rather than RRs. SAPALD is the only study that has results for both lifetime and current asthma.

Passive smoking exposure. The commonest exposure type is household exposure, with 45 RRs from 13 studies. For total exposure, there are 40 RRs from six studies with questionnaire-assessed exposure (mainly home and/or work), and only four RRs from one study (BECKE2) for biochemically-assessed (serum cotinine) exposure. The remaining 28 RRs from eight studies are for workplace exposure.

The most frequent timing of the passive smoke exposure is current, with 53 RRs from 10 studies, followed by lifetime exposure with 41 RRs from three studies. For study THORN, exposure was while living at 6 most recent homes and before diagnosis of asthma. There are also 10 RRs from four studies which refer to childhood exposure (regardless of adult exposure).

For most RRs, the denominator group comprises all those not exposed as defined for the numerator. The exceptions were four RRs from study JANSON, where exposure was from a specific household member (mother or father) but the denominator was no household exposure, and five RRs from study ROBBIN which refer separately to childhood, adulthood or both exposures relative to neither exposure.

Dose-response. Most of the categorical dose-response data come from study JAAKK3, which has 36 RRs comprising six sets of 2 categories, by number of cigarettes exposed to, and six sets of 4 categories, by pack-years. Additionally, studies JANSON and LARSS2 each have one set of 3 categories, by hours per day exposed, and study NG has two sets of 2 categories, by number of cigarettes smoked in the household.

Seven RRs from studies SAPALD and ROBBIN hold results regarding the dose-response relationship which could not be expressed in the usual categorical format (Table 8.6).

Table 8.6. Other dose-response results – non-smoking adults

Study	Asthma	Sex	Exposure	Adjusted	Results
SAPALD	lifetime	both	home/work	yes	Hours per day, significant p=0.0081 Number of smokers, significant p=0.028 (Hours per day × number of smokers also shown graphically without CI) Years, significant p=0.0246
ROBBIN	incidence	male	workplace	yes	At 1992 follow-up: years worked with smoker, not significant, excluded from final MLR model; mean 11.3 (cases), 7.8 (non-cases) p=0.162. Alternative (1987 follow-up) RR per 10 years worked with smoker is 1.50 (1.12-2.01)
		female	workplace	yes	At 1992 follow-up: RR per 7 years worked with smoker is 1.21 (1.04-1.39); mean 7.4 (cases), 4.6 (non-cases) p=0.023. Alternative (1987 follow-up) RR per 10 years worked with smoker is 1.50 (1.17-1.92)
		male	household	yes	At 1992 follow-up: years lived with smoker, not significant, excluded from final MLR model; mean 13.5 (cases), 7.7 (non-cases) p=0.039. Also excluded from final MLR model for 1987 follow-up.
		female	household	yes	At 1992 follow-up: years lived with smoker, not significant, excluded from final MLR model; mean 14.0 (cases), 11.9 (non-cases) p=0.254. Also excluded from final MLR model for 1987 follow-up.

MLR = multiple logistic regression.

Adjustment. 75 RRs have some adjustment. In all cases, this includes adjustment for age. 59 (64% of sexes-combined RRs) are adjusted for sex. The adjusted RRs come from 13 studies, and five studies only have adjusted RRs.

Two studies only have RRs adjusted for other sources of ETS (JANSON where RRs for current exposure are adjusted for childhood exposure and vice versa; and LARSS2 where RRs for workplace exposure are adjusted for household exposure).

2 × 2 table. The full 2 × 2 table is available for 40 of the 42 unadjusted RRs and the numbers of cases for another one. Among the adjusted RRs, the numbers of cases are available for 36 (48%). There are six studies which do not have the numbers of cases for any RR.

RR and CI. Apart from the seven non-categorical dose-response results already mentioned, six RRs have no values for the RR or CI, having only a statement of non-significance (none were significant). Two studies (KRONQV, PLATTS) have no RRs with values for the RR or CI.

The RR values range from 0.30 to 4.80.

The centrality of the RR in the CI was checked as described in §7.9. The value of C was outside the range 0.95 - 1.05 for only one RR, from study THORN, where it was 0.907. The RR/CI were given originally to only one decimal place, so the difference is probably due to rounding error.

For case-control and cross-sectional studies, the minimum number of cases and the total number of subjects implied by the CI (Lee, 1999) are compared with the actual numbers, as entered in the study database. No RRs showed a problem by this test. For analyses of prospective studies, the equivalent check on the number of cases is only approximate (see formula 16 of Lee, 1999) and again there were no RRs where a problem was seen.

Derivation method. 86 RRs are either as given originally, or are calculated directly from the numbers in the 2 × 2 table. For a further two RRs where both the 2 × 2 table and the RR and CI were originally available, the RR and CI are recalculated because of a discrepancy and four are calculated after summing categories to obtain a 2 × 2 table. The remaining 12 were estimated using a method for combining non-independent estimates (Fry & Lee, 2000).

8.3. THE META-ANALYSES

8.3.1. Introduction

The process of selecting which RRs to include in an analysis based on “preferences” and the combining of the RRs (Fleiss & Gross, 1991) are as described in §7.10.1 and §7.10.2.

The tables relate to two broad types of meta-analysis, as follows:

A) Any exposure
B) By amount of exposure

Results from Tables A and B are discussed, respectively, in §8.3.2 and §8.3.3, the tables themselves being included at the end of this chapter.

The layout of the tables is as described in §7.10.3. Briefly, each meta-analysis table has a preamble followed by results based on the "adjusted" data. The preamble describes the restrictions on the data included, the order of preference for selecting RRs to be included and a short description of the contents of the table. Appendix Tables A and B giving extended versions of the analyses are available at *www.pnlee.co.uk/etsast.htm*. They include a cover page and 7 sections – the cover page and section 3 are the same as the tables presented here. Sections 1-2 give more of the "adjusted analysis," sections 4-6 relate to the "unadjusted analysis" and section 7 gives additional information related to studies and RRs excluded from the meta-analysis. Thus the reader who wishes only to see the main meta-analysis estimates need refer only to the Tables, but the more interested reader who wishes to see full details of the individual RRs contributing to the estimates should refer to the corresponding Appendix Tables. The two sets of output always correspond directly.

Chapter 7 also provides information on some general restrictions to the analyses (in §7.10.4), the various ways outcome and exposure are defined (§7.10.5) the various factors considered in the analysis (§7.10.6), how meta-analyses by amount of exposure are conducted (§7.10.7) and certain conventions used in presenting the findings in this chapter (§7.10.9).

8.3.2. Risk from any Exposure – Table A and Appendix Table A

All analyses considered in §8.3.2 and presented in Table A (also presented in more detail in Appendix Table A) relate to the exposed/unexposed comparison and are not concerned with the extent of the exposure. "Exposure" may be defined as household members smoking, irrespective of whether this is actually in the presence of the subject. The various analyses summarized in Table A are shown in Table 8.7.

Table 8.7. Analyses summarized in Table A – non-smoking adults

Table	Definition of asthma outcome	Source of ETS exposure	Time of ETS exposure	Definition of non-smoking
A1	Lifetime/current	Total (or nearest)	Earliest	Never/non
A2	Lifetime/current	Total (or nearest)	Earliest	Never
A3	Lifetime/current	Total (or nearest)	Most recent	Never/non
A4	Lifetime/current	Total (or nearest)	Childhood	Never/non
A5	Lifetime/current	Total (or nearest), preferring paternal to maternal	Childhood	Never/non
A6	Current/lifetime	Total (or nearest)	Earliest	Never/non
A7	Lifetime/current	Household	Earliest	Never/non
A8	Lifetime/current	Household	Most recent	Never/non
A9	Lifetime/current	Workplace	Earliest	Never/non
A10	Lifetime/current	Workplace	Most recent	Never/non

Terms are defined in §7.10.5.

Thus Tables A1, A7 and A9 are the key analyses for the three main sources of exposure, choosing the earliest available exposure, each with a variant choosing the most recent exposure available (A3, A8, A10). Additionally A2 is based on a subset of the results in A1, restricted to studies which excluded ex-smokers, Tables A4 and A5 are variants restricted to exposure in childhood, and Table A6 is a variant choosing current asthma in preference to lifetime for study SAPALD.

Total Exposure: Tables A1, A3 and A6

The choice of total exposure index involves the following order of preference: total-biochemical; total-questionnaire; any household member; mother; workplace. For only one study (BECKE2) are total-biochemical results available (and these are the only result available for that study), while for most of the studies, preferencing led to inclusion of exposure from any household member. Exposure from mother was not chosen by the preferencing for any study, and workplace exposure was chosen for one study (LARSS2). For studies JANSON and LARSS2, results adjusted for other ETS exposure (childhood and household, respectively) are included, being the only results available.

Figure 8.1 presents the 18 RRs from the 14 studies included in the adjusted meta-analysis in Table A1. 15 are >1.00, of which three (LARSS1, SAPALD, THORN-males) are significantly positive ($p<0.05$), and three are <1.00, of which one (BECKE2-baseline prevalence) is borderline significantly negative ($p=0.05$). Overall there is a significant increased risk in relation to total exposure, with the RR estimate 1.14 (1.06-1.23, $p<0.001$) from the fixed effects model or 1.19 (1.04-1.35, $p<0.05$) from the random effects model. In the unadjusted analysis (see Appendix Table A1) alternative RRs were available from seven of the studies. Results are similar, with three of the 17 RRs significantly positive (THORN having only sexes-combined results here), and none significantly negative (BECKE2 just losing significance, $p=0.06$). The overall RR estimate is 1.16 (1.08-1.24, $p<0.001$) from the fixed effects model and 1.17 (1.04-1.32, $p<0.01$) from the random effects model. In the following text, we restrict attention to the adjusted analysis.

Egger's test (Egger et al., 1997) showed no evidence of publication bias. The heterogeneity chisquared is 37.20 on 17 d.f. ($p<0.01$). The excess of the chisquared over the degrees of freedom is not obviously explained by any specific outlying study, the largest Q_s values being 10.22 for the THORN-males result (where the lower confidence limit of 2.00 for the RR of 4.80 is higher than any of the other RRs), 8.22 for BECKE2-baseline and 6.74 for LARSS1. By far the largest weights are for study MISHRA, with males – RR = 1.20 (0.80-1.59), weight = 102 and females – RR = 1.05 (0.91-1.21), weight = 189, together accounting for 43% of the total weight of 672.

An alternative RR which would have been chosen as higher preference except that it was incomplete was available for study LARSS2. This referred to household exposure and merely stated that there was no significant increase[6] (thus suggesting no difference from the non-significant increase for workplace exposure included in Table A1). Two other studies (KRONQV and PLATTS) provide only incomplete data, both not significant with no further details.

[6] In the original paper (Larsson et al., 2003) this is given "for respiratory symptoms" but the context suggests this relates specifically to asthma.

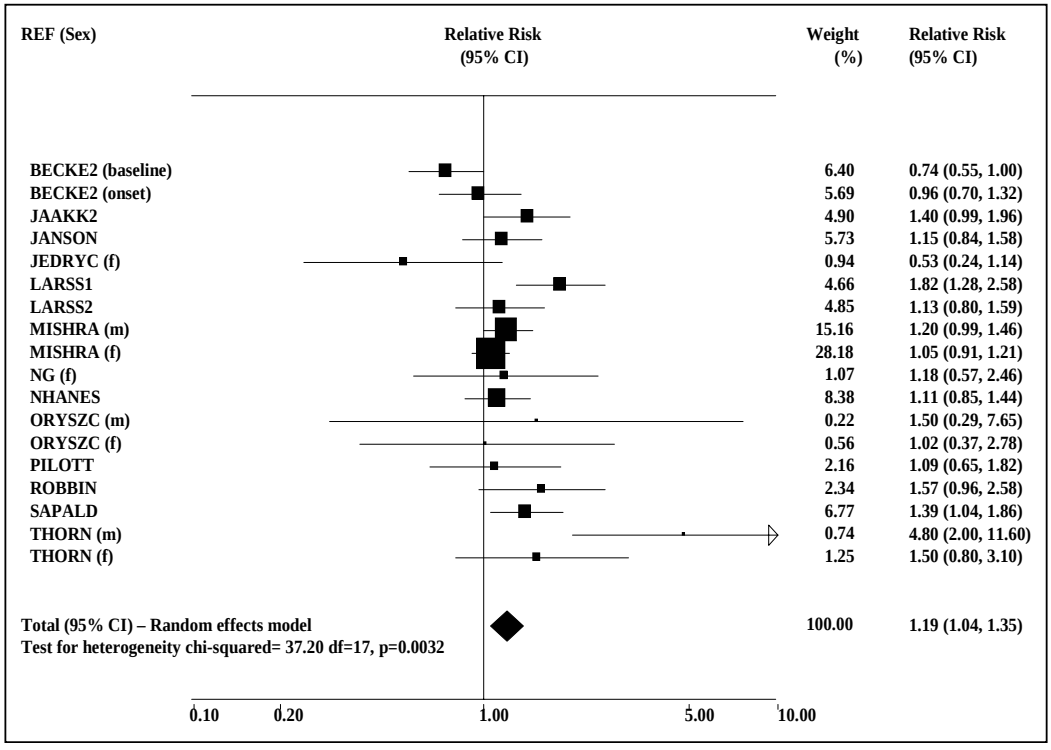

Figure 8.1. Forest plot for total exposure – non-smoking adults.[1]

[1] Asthma outcome: lifetime/current; source of ETS exposure: total (or nearest equivalent); time of ETS exposure: earliest; definition of non-smoking: never/non; these terms are defined in §7.10.5. Data as used in Table A1. The RRs used are adjusted for covariates where adjusted data are available.

Variation in RR by various factors is shown in Table A1, although the small number of studies available limits the usefulness of the comparisons that can be made, and results are heavily influenced by which factor level study MISHRA falls in.

Sex. Although the increase seen in females is not significant, the RR does not differ significantly from the estimates for males or for sexes combined.

Asthma definition. The increase in risk is significant for studies of both lifetime/incident asthma (1.20, 1.06-1.36, $p<0.01$) and current asthma (1.12, 1.02-1.22, $p<0.05$), and the difference between them is not significant. Only study SAPALD presented results for both definitions of asthma, and when current asthma was chosen in preference for that study (Table A6) the RR for lifetime/incident asthma reduced slightly and the RR for current asthma increased slightly, but the overall RR remained virtually unchanged (1.14, 1.06-1.24, $p<0.001$). There was also no difference seen between physician diagnosed asthma and other.

Location. The estimates vary significantly ($p<0.01$) by continent, with the RR from the European studies (1.40, 1.21-1.63) significantly higher than from the US studies (0.99, 0.84-1.16).

Timing of study. There is weak evidence that risk estimates are higher in studies which started later than in earlier studies ($0.05<p<0.1$), but the difference is in the opposite direction and non-significant when based on publication year.

Table 8.8. Odds ratios (95% CIs) for asthma, women, study JANSON – non-smoking adults

	Never smokers	Ex-smokers[1]
Paternal smoking	0.67 (0.49-0.91)	0.88 (0.53-1.48)
Maternal smoking	1.10 (0.78-1.55)	1.17 (0.78-1.55)

[1] Not entered on database.

Study type and analysis type. There is significant evidence of heterogeneity due to study type (χ^2 = 9.32 on 2 d.f., p<0.01), with the highest estimates in case-control studies (1.56, 1.19-2.05, n=5), intermediate in cross-sectional studies (1.15, 1.06-1.26, n=10) and lowest in prospective studies (0.93, 0.76-1.13, n=3). However the RR from the prospective studies is non-significantly >1.00 if the analysis is restricted to onset of asthma (1.11, 0.85-1.45, n=2, studies BECKE2 and ROBBIN, omitting BECKE2 baseline-prevalence, data not shown). There is also no evidence of a difference between prevalence (1.13, 1.05-1.23, n=15) and onset (1.21, 0.98-1.49, n=3) where the latter category includes the case-control study JAAKK3 (first episode of asthma).

Ex-smokers. There is significant heterogeneity (χ^2 = 4.23 on 1 d.f., p<0.05), with an increased RR seen only in those studies which excluded ex-smokers (1.20, 1.10-1.31, n=13) and not in those which included them (1.00, 0.86-1.16, n=5). The two studies which reported results separately for ex-smokers and never smokers shed little light on this difference. Study KRONQV merely reported no significant association in either ex-smokers or never smokers. Study JANSON did not report results for male ex-smokers because of small numbers, while the risks reported for female ex-smokers were slightly higher than the equivalent results for female never smokers, but still not significant, as shown in Table 8.8.

Analysis restricted to the studies excluding ex-smokers is discussed below (subsection Total exposure in never smokers).

Age. Although there is some evidence of heterogeneity (0.05<p<0.1 for lowest age in study, and p<0.05 for highest age), the RR is highest in studies falling in the middle category and this is probably not indicative of any real effect of age on risk.

Size of study. There is significant heterogeneity (χ^2 = 13.68 on 3 d.f., p<0.01), with an increased risk seen in smaller studies (1.40, 1.05-1.86, p<0.05 from studies with up to 100 cases, and 1.50, 1.25-1.81, p<0.001 from studies of 101-400 cases), but not in the largest studies (1.05, 0.95-1.15, NS). This represents a significant trend (p<0.01[7])

Adjustment for confounding variables. There is little evidence of heterogeneity according to whether the study took into account specific factors as potential confounder, to whether the RR itself was adjusted for specific factors, or to the number of factors the RR was adjusted for.

Source of exposure. There is some evidence of heterogeneity by source of exposure (χ^2 = 11.26 on 3 d.f., p<0.05), largely due to the low estimates for total-biochemical arising from study BECKE2 (0.84, 0.67-1.04, n=2). The estimates for both total-questionnaire (1.34, 1.13-1.59, n=4) and household (1.16, 1.05-1.27, n=11) are significantly >1.00. As described earlier, the choice of total exposure index was based on an order of preference; analyses

[7] Based on additional analysis (full details not shown) using trend coefficients of 1, 2, 3.

specifically restricted to household and workplace exposures are discussed later in this section.

Timing of exposure. In Table A1 the preferencing favoured the earliest exposure in the subject's life (after having chosen the most general source of exposure available as described in the previous paragraph), as follows: childhood; lifetime; adulthood; recent (last 6 homes); unspecified; current. Adulthood and recent were combined in one factor level (and in fact only recent was chosen by the preferencing – study THORN). Despite being the lowest preference, current exposure is the most commonly selected (11 RRs). There is evidence of heterogeneity by time of exposure (χ^2 = 18.11 on 4 d.f., p<0.01). Risk from current exposure (1.07, 0.99-1.17, n=11) was not significantly >1.00, and was significantly lower than exposure in adulthood (2.31, 1.35-3.96, n=2, study THORN) or in childhood (1.73, 1.30-2.31, n=2, studies LARSS1 and ROBBIN).

In the variant Table A3 the preferencing favoured the most recent exposure. In fact, the RR altered only for two studies as compared to Table A1, choosing current exposure rather than lifetime for study JAAKK3, and adult rather than childhood for study ROBBIN. This increased the overall estimate of risk slightly, to 1.15 (1.07-1.24) for the fixed effects model and 1.21 (1.05-1.40) for the random effects model. Heterogeneity remained similar (χ^2 = 17.41 on 4 d.f., p<0.01), with risk from studies of current exposure now marginally significantly increased (1.09, 1.01-1.19, n=12), but still significantly lower than for adult exposure (1.99, 1.40-2.83, n=3, studies ROBBIN, THORN) or childhood (n=1, LARSS1) exposure.

Exposure specifically in childhood is discussed below (subsection Total exposure in childhood).

Derivation of RR/CI. There is no evidence of heterogeneity according to whether the RR was available directly (n=11), had been calculated directly from the numbers in the 2 × 2 table (n=3), or had been calculated by combining over strata (n=4).

Thus the main sources of heterogeneity appear to be the *higher* estimates of risk from studies conducted in Europe rather than elsewhere, and from case-control studies rather than cross-sectional or prospective studies; and *lower* estimates from studies that included rather than excluded ex-smokers (i.e. restricted to non-smokers rather than to never smokers), from studies that considered biochemical rather than questionnaire assessed exposure, and from studies that considered current exposure rather than earlier or more general exposure timings. However these factors may not be acting independently, with for instance, biochemical exposure inherently current, all case-control studies conducted in Europe, and all prospective studies including ex-smokers, and it is difficult to distinguish between these effects given the small number of studies available.

Total Exposure in Never Smokers: Table A2

The meta-analysis of Table A1 is repeated in Table A2, but restricted to those studies that excluded ex-smokers, i.e. were restricted to never (or almost never) smokers. Thus 13 RR estimates are included in the adjusted analysis, of which 12 are >1.00 (three significantly so), and one is non-significantly <1.00. As has already been noted, the overall fixed effects adjusted RR from this group of studies is higher than from all the studies, 1.20 (1.10-1.31), and this is also the case for the random effects model, 1.27 (1.09-1.49), and for the unadjusted analysis, 1.20 (1.11-1.29) for the fixed effects model and 1.24 (1.09-1.42) for the random

effects model. Again, we now restrict attention to the adjusted analysis. Heterogeneity remains significant (χ^2 = 25.13 on 12 d.f), with study THORN again the main contributor, with its Q_S value now 9.58. Study MISHRA now represents 58% of the total weight.

The variation in RR was examined only for some of the key factors. Even with this reduced list of factors, the usefulness of the analysis is limited, with no studies conducted in US, started before 1990, or of prospective design. Differences seen previously which remain are the higher ($p<0.05$) RR for case-control (1.56, 1.19-2.05, n=5) rather than cross-sectional studies (1.16, 1.06-1.27, n=8), and the higher ($p<0.05$) RR from studies conducted in Europe (1.40, 1.21-1.63, n=9) rather than elsewhere (1.11, 1.00-1.23, n=4). Additionally, there is now also evidence of heterogeneity due to sex (χ^2 = 6.96 on 2 d.f., $p<0.05$) although the pattern is in fact very similar to that seen previously for all studies, and also due to asthma definition (χ^2 = 7.70 on 1 d.f. $p<0.001$), where the estimate from studies of lifetime asthma is now significantly higher (1.49, 1.25-1.78, n=5) than from studies of current asthma (1.12, 1.01-1.23, n=8).

Total Exposure in Childhood: Tables A4 and A5

Four studies gave results for exposure in childhood, of which one, KRONQV provided results insufficient to include in meta-analysis (not significant with no further details). Thus results from three studies are available. Exposures considered were total (ROBBIN), any household member (LARSS1) and parental (JANSON). For study JANSON, maternal smoking was chosen for Table A4 and paternal for Table A5; only results adjusted for current ETS exposure are available for this study.

The estimates from studies LARSS1 and ROBBIN included in both tables are >1.00, significantly ($p<0.001$) so for LARSS1, and these are in fact the same estimates as chosen from these studies for Table A1. The estimates for maternal exposure (Table A4) from study JANSON are both non-significant, with the male estimate <1.00 and the female >1.00, whereas for paternal exposure (Table A5) they are in the opposite direction and the decrease for females is significant ($p=0.01$). The overall RR estimates from these meta-analyses are all >1.00, but this is only significant ($p<0.05$) when both the fixed effects model and maternal exposure are chosen. It can also be noted that study RAHERI (excluded from the meta-analysis because it is a subset of study JANSON) reported a significant decrease in risk of lifetime asthma associated with childhood exposure (0.30, 0.14-0.61, $p<0.005$).

Variation in RR by the key factors is shown in Tables A4 and A5, but the number of studies available is too small to allow any conclusions to be drawn.

It is also of interest to note that study ROBBIN reported results for childhood and adulthood separately, both against a base of no exposure at either time. These results, shown in Table 8.9, are not suggestive of any effect of childhood exposure given adult exposure.

Table 8.9. Odds ratios (95% CIs) for asthma onset from multiple logistic regression, study ROBBIN – non-smoking adults

	Unexposed in childhood	Exposed in childhood
Unexposed in adulthood	1.00 (base)	0.74 (0.26-2.06)
Exposed in adulthood	1.57 (0.81-2.97)	1.89 (1.13-3.15)

Household Exposure: Tables A7 and A8

Ten studies provide results for household exposure. For two studies, only RRs adjusted for other ETS exposure (for workplace exposure for JAAKK3 [adjusted analysis] and for current exposure for JANSON) are available. With a preference favouring earliest exposure (Table A7), the adjusted meta-analysis includes 14 RRs, all but three of which (from studies JAAKK3 and JANSON) are in fact the same as those included in Table A1. The overall estimate shows a significantly increased RR, 1.13 (1.04-1.23, $p<0.01$) from the fixed effects model or 1.16 (1.00-1.35, $p=0.05$) from the random effects model, which, not surprisingly, is quite similar to the total exposure estimate (Table A1). Heterogeneity also remains quite similar ($\chi^2 = 25.99$ on 13 d.f., $p<0.05$). Analyses studying the variation in RR are presented only for the key factors. The pattern of variation is similar to that previously seen, although the only factor showing significant evidence of heterogeneity is definition of asthma ($\chi^2 = 10.87$ on 1 d.f., $p<0.001$), with a significantly elevated risk seen only from studies of lifetime asthma (1.69, 1.31-2.19, n=4) and not from studies of current asthma (1.07, 0.98-1.18, n=10).

The variant analysis preferring most recent exposure (Table A8) also differs from the total exposure analysis only in the RRs selected for studies JAAKK3 and JANSON. The estimate for JAAKK3 is higher (4.77, 1.29-17.70) than that used in Table A3 (1.97, 1.19-3.25) or Table A7 (1.09, 0.77-1.53). This results in higher overall estimates, slightly for the fixed effects model (1.17, 1.06-1.28) and more so for the random effects model (1.26, 1.05-1.53). However the heterogeneity ($\chi^2 = 27.62$ on 12 d.f., $p<0.01$) and the pattern of results by key factors are not dissimilar from that seen for total exposure (Table A3).

Workplace Exposure: Tables A9 and A10

Eight studies gave results for workplace exposure. Studies KRONQV and SAPALD simply reported no significant association without further details, and study ROBBIN reported only trend analyses which are discussed later (§8.3.3). Thus, results suitable for meta-analysis are available from five studies. For study LARSS2, the exposure was strictly *"in smoky rooms outside your home,"* but we follow the original authors who state that this *"mainly related to work, since most of the subjects were of working age"* (Larsson et al., 2003). For three studies, only results adjusted for other ETS exposure (for household exposure for JAAKK3 [adjusted analysis] and LARSS2, and for childhood exposure for JANSON) are available.

In the adjusted meta-analysis preferring earliest exposure (Table A9, Figure 8.2), there are six estimates, of which four are >1.00, three of them significantly so, and two, both from study ORYSZC, are non-significantly <1.00. Study NHANE3 has the largest weight and represents 48% of the total weight. The overall estimate of risk is highly significantly increased, 1.37 (1.18-1.59, $p<0.001$) from the fixed effects model or 1.36 (1.09-1.70, $p<0.01$) from the random effects model. There is no evidence of heterogeneity ($\chi^2 = 7.97$ on 5 d.f., $p>0.1$). Analyses studying the variation in RR are presented by the key factors, but as expected when the overall heterogeneity is non-significant, none of the factors showed any significant variation.

The unadjusted analysis preferring earliest exposure (Appendix Table A9), and the variant analyses preferring most recent exposure (Table A10), differ only in the RRs selected from study JAAKK3 (Table A9 1.55 adjusted or 1.25 unadjusted; Table A10 2.16 adjusted or 1.87 unadjusted). The overall estimates using the adjusted data, 1.39 (1.19-1.63, $p<0.001$)

from the fixed effects model and 1.40 (1.06-1.85, p<0.05) from the random effects model, are similar to those in Table A9.

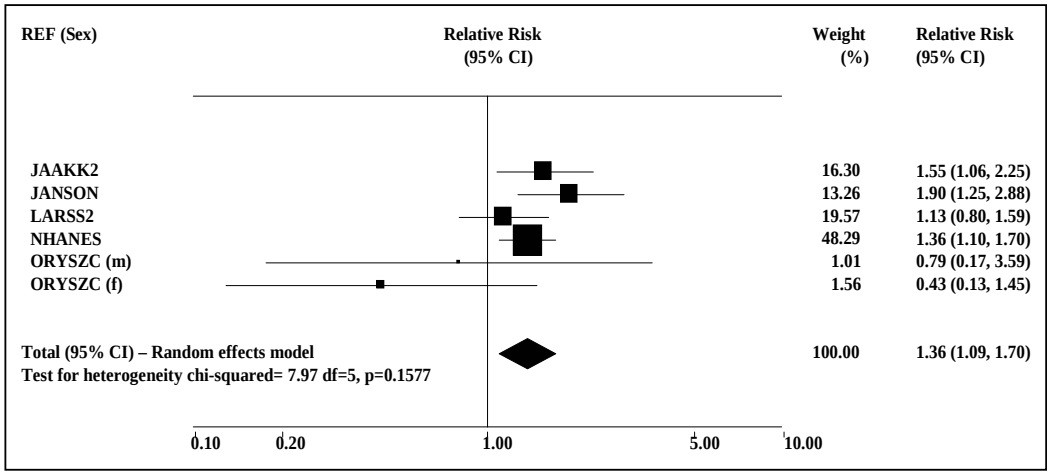

Figure 8.2. Forest plot for workplace exposure – non-smoking adults.[1]

[1] Asthma outcome: lifetime/current; source of ETS exposure: workplace; time of ETS exposure: earliest; definition of non-smoking: never/non; these terms are defined in §7.10.5. Data as used in Table A9. The RRs used are adjusted for covariates where adjusted data are available.

8.3.3. Risk by Amount of Exposure – Table B and Appendix Table B

The analyses considered in §8.3.3 and presented in Table B (also presented in more detail in Appendix Table B) form pairs, with the first of each pair relating to a "low dose" versus unexposed comparison, and the second relating to a "high dose" versus unexposed comparison. The various analyses summarized in Table B are shown in Table 8.10.

Table 8.10. Analyses summarized in Table B – non-smoking adults

Table	Source of ETS exposure	Measure of dose	Dose
B1	Total (or nearest)	Cigarettes or hours	Low
B2	Total (or nearest)	Cigarettes or hours	High
B3	Household	Cigarettes or hours	Low
B4	Household	Cigarettes or hours	High
B5	Workplace	Cigarettes or hours	Low
B6	Workplace	Cigarettes or hours	High
B7	Total (or nearest)	Pack-year, cigarettes or hours	Low
B8	Total (or nearest)	Pack-year, cigarettes or hours	High
B9	Household	Pack-year, cigarettes or hours	Low
B10	Household	Pack-year, cigarettes or hours	High
B11	Workplace	Pack-year, cigarettes or hours	Low
B12	Workplace	Pack-year, cigarettes or hours	High

Terms for source of exposure are defined in §7.10.5.

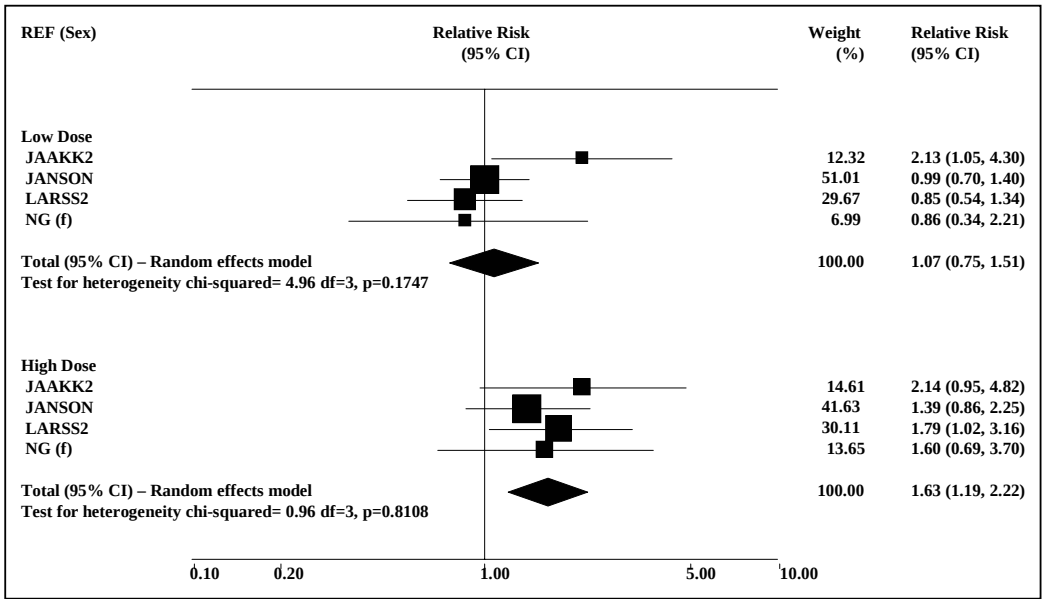

Figure 8.3. Forest plot for total exposure by amount – non-smoking adults.[1]

[1] Asthma outcome: lifetime/current; source of ETS exposure: total (or nearest equivalent); measure of dose: cigarettes or hours per day; these terms are defined in §7.10.5. Data as used in Tables B1 and B2. The RRs used are adjusted for covariates where adjusted data are available.

Because only study JAAKK3 has a choice of results available for different exposures and measures of dose, the RRs chosen for each pair of tables differ only for that study. All studies with relevant results excluded ex-smokers, and no study had a choice of results for asthma definition or (given the exposure measure) exposure time.

In all cases, the overall RR estimate for low dose does not differ significantly from 1.00, whereas that for high dose generally shows a significant increase. For instance, for total exposure (or nearest available) and preferring numbers of cigarettes for study JAAKK3, the overall adjusted fixed effects estimate is 1.03 (0.80-1.32, NS, n=4) for low dose and 1.63 (1.19-2.22, $p<0.01$, n=4) for high dose (Tables B1, B2, Figure 8.3). Similarly when restricted to workplace exposure, the adjusted fixed effects estimate is 1.08 (0.73-1.59, NS, n=2) for low dose and 2.04 (1.26-3.31, $p<0.01$, n=2) for high dose (Tables B5, B6). The only exception is the analysis restricted to household exposure and preferring numbers of cigarettes for study JAAKK3, where neither the low nor high dose estimate differs significantly from 1.00, and, for the random effects model, the high dose estimate is actually slightly lower than the low dose estimate (Tables B3, B4). However when pack-years is preferred as the measure of exposure for study JAAKK3, then the usual pattern is again seen for household exposure, although the significance of the high dose increase is weaker ($0.05<p<0.1$) (Tables B9, B10).

The dose-response data considered in Table B derive only from those four studies (JAAKK3, JANSON, LARSS2, NG) which present RRs by level of exposure. As noted earlier, two studies also presented results of dose-response analyses expressed as an increase in risk per unit of exposure. As shown in Table 8.6, study SAPALD reported a significant trend with home/work exposure, whether expressed in terms of hours per day exposed ($p<0.01$), number of smokers exposed to ($p<0.05$) or years of exposure ($p<0.05$). Study

ROBBIN, in the 1992 follow-up data, reported a significant association with years worked with a smoker in females ($p<0.05$) but not males, and a significant association with years lived with a smoker in males ($p<0.05$) but not females.

Taken together the data considered in Table B and in Table 8.6 demonstrate the existence of a dose-response relationship.

Table 8.11. Summary of analyses for ETS exposure (irrespective of amount smoked) – non-smoking adults

Table	Source of exposure[1]	Timing of exposure[1]	Variant[2]	N[3]	Fixed effects RR (95% CI)[4]	Random effects RR (95% CI)[4]	Heterogeneity Chisq per df[5]
A1	Total	Earliest		18	1.14 (1.06-1.23)	1.19 (1.04-1.35)	2.19**
A2	Total	Earliest	No ex-smoker	13	1.20 (1.10-1.31)	1.27 (1.09-1.49)	2.09*
A3	Total	Most recent		18	1.15 (1.07-1.24)	1.21 (1.05-1.40)	2.48***
A4	Total	Childhood		4	1.27 (1.04-1.54)	1.26 (0.88-1.81)	3.34*
A5	Total	Childhood	Paternal	4	1.11 (0.93-1.33)	1.18 (0.74-1.90)	6.59***
A6	Total	Earliest	Current/ Lifetime	18	1.14 (1.06-1.24)	1.20 (1.04-1.37)	2.27**
A7	Household	Earliest		14	1.13 (1.04-1.23)	1.16 (1.00-1.35)	2.00*
A8	Household	Most recent		13	1.17 (1.06-1.28)	1.26 (1.05-1.53)	2.30**
A9	Workplace	Earliest		6	1.37 (1.18-1.59)	1.36 (1.09-1.70)	1.59 NS
A10	Workplace	Most recent		6	1.39 (1.19-1.63)	1.40 (1.06-1.85)	2.05(*)

[1] Terms are defined in §7.10.5. Total includes nearest equivalent.

[2] Variant: Except for Table A2 analyses may include results for non-smokers if estimates for never smokers are not available. Except for Table A5 estimates for maternal exposure are preferred to estimates for paternal exposure; except for Table A6 estimates for lifetime asthma are preferred to estimates for current asthma. In Tables A5 and A6 the reverse preferences are used.

[3] N = number of RR estimates combined.

[4] The RRs used are adjusted for covariates where adjusted data are available.

[5] Significance of heterogeneity: *** $p<0.001$, ** $p<0.01$, * $p<0.05$, (*) $p<0.1$, NS $p\geq0.1$.

8.4. DISCUSSION

8.4.1. Evidence of an Association

Table 8.11 summarizes the results of the analyses relating asthma to ETS exposure (irrespective of amount) presented in Tables A1-A10 and discussed in §8.3.2. The analyses show an increased risk of asthma in the ETS-exposed group, which is always significant except for some of the estimates for childhood exposure, which are based on limited data. The meta-analysis estimates are all consistent with a weak association, with risk about 20% higher in the ETS-exposed group, the slightly higher estimates for workplace exposure having a relatively wide CI. There is no clear indication that RR estimates vary by type of meta-analysis (fixed effects or random effects), source of exposure (total, household, workplace), timing of exposure (earliest, most recent, childhood), by whether ex-smokers are included or excluded from analysis, by whether preference is given to results for lifetime or current asthma or by whether, when childhood exposure is considered, estimates for maternal or paternal smoking are used. The RR estimates used in Table 8.11 are adjusted for covariates, where adjusted estimates are available. The same conclusions would have been reached had preference been given to unadjusted estimates.

It should be noted that some of the similarity in the meta-analysis estimates in Table 8.11 arises because, for 8 out of 14 of the studies providing data, only a single adjusted RR was available, and this RR contributed to a number of the meta-analyses. Of the other six studies, four provided only two RRs, and only for studies JAAKK3 and JANSON were a relatively large number of alternative RRs available.

8.4.2. Evidence of a Dose-response Relationship

The data available are rather limited, with only four studies providing estimates by level of exposure and two studies providing results of trend analyses. Of the four studies giving data by level of exposure, three only provided a single pair of estimates (for low and high exposure) and only for study JAAKK3, and the two studies providing trend data (SAPALD, ROBBIN) were data available for a variety of ETS exposure sources and measures.

The data for low exposure analysed in Table B consistently show no significant evidence of an increased risk of asthma associated with ETS exposure. The data for high exposure, however, do show a significant increase, a finding which is supported by significant trends seen in studies SAPALD and ROBBIN. The relevant data for total exposure (or nearest equivalent) are summarized in Table 8.12. Using alternative ETS exposure sources and measures does not affect the general conclusion that the data do provide evidence of an increased risk at higher ETS exposures.

Clearly the data available show an association and a dose-response relationship that, at least for a number of the exposure indices, cannot be explained by chance. In order to interpret these findings, it is necessary to consider various aspects of the data further.

Table 8.12. Dose-response data for total ETS exposure (or nearest equivalent) – non-smoking adults

Study	Sex	Exposure	Level	Relative risk (95% CI)[1]
JAAKK3	M+F	Current, at home or work	1-9 cigs/day	2.13 (1.05-4.30)
			10+ cigs/day	2.14 (0.95-4.82)
JANSON	M+F	Current, at home or work	<4 hours/day	0.99 (0.70-1.40)
			4-7 hrs/day	1.19 (0.76-1.88)
			8+ hrs/day	1.39 (0.86-2.25)
LARSS2	M+F	Current, at work[2]	<1 hrs/day	0.85 (0.54-1.34)
			1-5 hrs/day	1.21 (0.71-2.07)
			6+ hrs/day	1.79 (1.02-3.16)
NG	F	Lifetime, at home	1-19 cigs/day[3]	0.86 (0.34-2.21)
			20+ cigs/day	1.60 (0.69-3.70)
ROBBIN	M	Years lived with smoker	Non-cases	Mean 7.7
			Cases	Mean 13.5 ($p<0.05$)[4]
	F	Years lived with smoker	Non-cases	Mean 11.9
			Cases	Mean 14.0 (NS)[4]
SAPALD	M+F	Current, at home or work	Hours/day	Trend $p<0.01$
Random effects meta-analysis – based on first 4 studies			Low	1.07 (0.75-1.51)
			High	1.63 (1.19-2.22)

[1] Adjusted data if available, unless otherwise stated.

[2] Outside home but *"mainly related to work"* (Larsson et al., 2003).

[3] Maximum consumption of any household smoker.

[4] Means given are unadjusted; years lived with a smoker was omitted from multiple logistic regression analysis as not significant.

8.4.3. Consistency of Findings

As shown in Table 8.11, there is evidence of heterogeneity in all the Table A analyses, statistically significant except for the limited data for workplace ETS exposure. Identifying the sources of the heterogeneity is not straightforward, partly because one study (MISHRA), which contributes to the analyses in Tables A1-A3 and A6-A8, has a very large weight, and partly because there are studies with unusually high estimates (THORN, males, 4.80) and with unusually low estimates (JEDRYC, 0.53) for reasons that are not clear. Also the number of estimates available is rather small to allow detailed study of sources of heterogeneity.

We have investigated variation in risk on a one factor at a time basis, rather than on a multivariate basis, with Table A1 considering the largest number of factors. There, the most statistically significant ($p<0.01$) variations in estimate by factor level relates to:

- *continent*, with the strongest associations seen in studies conducted in Europe, and no clear association seen in studies conducted in the United States or elsewhere;
- *study type*, with the association strongest for case-control studies, intermediate for cross-sectional studies and not evident for prospective studies;

- *study size*, with the association strongest in the smaller studies (≤400 cases) and not evident in the larger studies (401+ cases) or in the studies with the number of asthma cases unknown; and
- *time of exposure*, with the association not really evident for current exposure or when the time was unspecified, but evident otherwise – whether the estimate was based on childhood, adult or lifetime exposure.

The extent to which these observed significant variations represent independent or meaningful differences is unclear, bearing in mind the relatively small number of estimates available at some factor levels (e.g. only three for prospective studies), and the likely interrelationships between the factors.

8.4.4. Publication Bias

Though there is a consistent association with a dose-response relationship, this does not of itself imply a cause and effect relationship. Sources of bias and confounding have to be considered. One such source of bias is publication bias. The traditional main sources of publication bias are authors being less willing to submit for publication, and journal editors being less willing to accept for publication, papers which report no association between exposure and disease than papers which report such an association. Publication bias can be investigated by various possible techniques, all of which involve assumptions which are difficult to justify formally.

In one approach, we find that large studies tended to give lower RR estimates than do small studies, suggesting the possibility that some publication bias may exist. This is supported by the observation that there were six cases where a lack of significant association of ETS exposure with asthma was noted, but results sufficient for inclusion in meta-analysis were not presented. However, formal testing using the Egger method (Egger et al., 1997) does not show any significant evidence of publication bias for any of the analyses considered in Appendix Table A. Noting also that 15 of the 18 estimates in Table A1 are greater than 1.0, it seems unlikely that publication bias could explain the whole association.

8.4.5. Diagnostic Bias

Ideally, an epidemiological study of the relationship of an exposure to a disease should involve a disease which has a clearly defined and generally accepted definition, with subjects defined as cases based on accurate diagnostic criteria. Inclusion of cases with other diseases may lead to over- or under-estimation of the relationship of interest, depending on the magnitude and direction of the relationship of the exposure to these other diseases.

While asthma is recognized as a chronic respiratory condition characterized by airway inflammation and episodic airflow limitation, clinical definitions of the disease vary. We specified at the outset that only studies where the endpoint was “asthma” were to be included, with studies of “wheeze,” “wheezing bronchitis” or “chronic wheezing” to be excluded. It

was further decided, in order to attempt to achieve consistency of definition, to exclude "asthma or wheeze" and "asthmatic bronchitis."

In practice, except for two studies (JANSON, MISHRA) where the asthma was self or proxy reported, the diagnosis of asthma was made by the physician, usually with the subject also reporting symptoms currently or in the last 12 months. This means that one cannot usefully investigate diagnostic bias by seeing how RRs vary by the source of diagnosis. It is possible that knowledge of ETS exposure may have affected the diagnosis but the data available provide no means to test this.

8.4.6. Representativeness

As noted in §8.1.4, most of the studies were of the general population with no major restrictions, except that one (ROBBIN) was of Seventh Day Adventists and another (KRONQV) was of farmers. Other restrictions are mainly of a minor nature. It is not evident how the association observed between ETS and asthma could have arisen due to use of unrepresentative populations.

8.4.7. Misclassification of Exposure

The only study to provide RR estimates based on biochemically-assessed exposure estimates was BECKE2, which used serum cotinine. Otherwise indices were questionnaire-assessed, based generally on exposure at home and/or at work. Though reported data are generally highly reliable, there is ample documentation that a small proportion of smokers deny smoking on interview (Lee & Forey, 1995) and also that reporting of smoking by others is not completely accurate. Random misclassification of exposed adults as unexposed (or of unexposed adults as exposed) will tend to lead to some underestimation of the true association of exposure with asthma. However, misclassification may not necessarily be random. If having asthma makes it more likely that ETS exposure will be reported (perhaps because the asthmatic is more aware of it), then the RR will be systematically overestimated.

If ETS exposure is recorded before onset of asthma, such systematic bias should not occur, but if it is recorded when the subject already has asthma it is more plausible. The observation that an association of ETS exposure with asthma was seen in case-control and cross-sectional studies, but not in prospective studies, might therefore at first sight suggest the association might be an artefact of systematic bias of this type. However, such an inference is far from reliable. The results for prospective studies are only based on two studies, and in one of these (ROBBIN) it is unclear whether the exposure measure used (based on repeated measurements throughout the study period) actually related to the period before asthma onset. It still remains possible that underestimation of the true relationship due to random misclassification of ETS exposure may be more important than any overestimation due to asthmatics overstating their exposure.

Another possible bias may arise because someone with asthma tends to avoid ETS exposure. If this were true, and ETS exposure caused asthma, one would expect to find a weaker association of asthma with post-onset ETS exposure than with pre-onset ETS exposure. As shown in Table 8.11, there is no marked difference in the meta-analysis

estimates, whether earliest or most recent ETS exposure is preferred (Table A1 vs A3 for total exposure; Table A7 vs A8 for household exposure and Table A9 vs A10 for workplace exposure). However, in fact only three studies had alternative estimates relating to differing timing of exposure, with no clear evidence that early or late exposure was more strongly associated with asthma. Some further issues relating to timing of ETS exposure are discussed in §8.4.11.

8.4.8. Smoking by the Subject

It has been claimed by some (e.g. Larsson, 1994; Beeh et al., 2001) that smoking increases the risk of asthma, though we have never carried out a detailed review of the subject. For that reason we sought data relating ETS exposure to asthma in adults who have never smoked. In practice, the data were so limited that we accepted also data for non-smokers (i.e. including ex-smokers). Of the 16 principal studies, 11 concerned self-reported never smokers (or those whose lifetime smoking history was less than a small defined amount), three concerned self-reported non-smokers, one based non-smoker status on biochemical assessment and one on a combination of self-report and biochemical assessment.

It is known that smoking habits in family members tend much more often to be concordant than would be expected by chance (Lee, 1992). There is also evidence of concordance of smoking habits between work colleagues (Lee et al., 2002). It thus follows that, compared to non-ETS-exposed non-smokers, ETS-exposed non-smokers will contain a higher frequency of ex-smokers and a slightly higher frequency of asthma as a result. Given also that a proportion of current smokers deny their smoking on interview (Lee & Forey, 1995), it also follows that ETS-exposed non-smokers (and never smokers) will contain a higher frequency of current smokers. The extent of such bias is difficult to assess, but is probably small, as any association of smoking with asthma seems not to be strong.

8.4.9. Confounding

Although the causes of asthma are not fully understood, there is a wide range of potential confounding variables that have been taken into account in at least some of the studies considered. Leaving aside other sources of exposure to tobacco smoke or its constituents, factors considered include the sex, age and race of the subject, location within the study area (including urban/rural or more/less polluted areas), education, occupation, body mass index, aspects of medical history of the subject and the family, cooking methods, household composition (e.g. number of siblings, marital status), housing quality, crowding and mould, pets and exposure to allergens. However some of these factors have only been considered in one or two studies and some other factors that might be considered important, such as diet, exercise, exposure to infections and use of air conditioning and humidifiers, have not been considered at all.

There are considerable problems in assessing the extent of confounding, particularly by individual variables. Many studies present only unadjusted or only adjusted RRs, while those that do present adjusted and unadjusted risks typically only provide estimates simultaneously adjusted for several potential confounding variables, so that the effect of adjustment for

specific variables cannot readily be assessed. Furthermore, in some studies, the RRs presented deliberately do not adjust for certain variables found in preliminary analyses not to have any material confounding effect.

The statistical analyses that we have conducted look at the issue of confounding using various methods.

One method that we use is to compare the results of alternative analyses, one using adjusted RRs where possible and unadjusted RRs otherwise, the other using unadjusted RRs where possible and adjusted RRs otherwise. In practice, results do not differ meaningfully between the two analyses. For example in the analyses of overall ETS exposure presented in Table A1 (and Appendix Table A2 sections 1-3), the meta-analysis estimates based on adjusted RRs where possible are 1.14 (1.06-1.23) using the fixed effects model and 1.19 (1.04-1.35) using the random effects model. In contrast the corresponding results using unadjusted risks where possible (Appendix Table A1 sections 4-6) are 1.16 (1.08-1.24) using the fixed effects model and 1.17 (1.04-1.32) using the random effects model. Looking at the detailed data, there were two studies that presented unadjusted data only, five studies that provided adjusted data only and seven studies that provided both. Of this latter group, adjustment increased the RR estimate in three studies (by 0.23, 0.20 and 0.06) and decreased the RR in four studies (by 0.08, 0.07, 0.02 and 0.02).[8] This does not indicate any consistent or major effect of confounder adjustment in these studies.

This conclusion is reinforced by analyses that showed that RRs did not vary systematically according to the number of confounding variables adjusted for, or whether specific confounding variables were adjusted for. However the relatively small number of studies considered, the variety of variables taken into account, and the fact that studies do not generally present the results of analysis adjusted and not adjusted for specific factors, and the fact that some variables are not considered by any studies at all mean that one cannot completely rule out the possibility that some confounding may exist. However any confounding effect is probably not large.

8.4.10. Smoking in Pregnancy

Some studies in children have attempted to separate out possible effects of ETS exposure and of maternal smoking in pregnancy. None of the studies of adults provide any results for *in utero* exposure. However in the study SAPALD there is a statement that *"Excluding subjects who reported that their mothers smoked at all in pregnancy ... had little impact. Some subjects may not reliably know whether their mothers smoked during pregnancy. They are more likely to know whether their mothers ever smoked, and the third column in Table 3 shows the impact of excluding all subjects whose mothers ever smoked."* From their Table 3 the odds ratio for asthma in relation to passive smoke exposure was 1.39 (1.04-1.86) including all the subjects, and 1.43 (1.04-1.96) excluding subjects whose mother ever smoked.

Failure to collect data on maternal smoking in pregnancy is a limitation of the studies considered as, in theory, it could be correlated both with risk of asthma and with indices of ETS exposure.

[8] Using combined sex estimates where separate male and female results are available.

8.4.11. Exacerbation or Induction?

In one model of asthma, people remain asthma-free until some exposure first induces symptoms of the disease and leads to the person being diagnosed as asthmatic. Subsequently other exposures (not necessarily to the same agent) may lead to exacerbation of the asthmatic symptoms. Studies that clearly relate to exacerbation have already been considered in chapters 3 to 6. Here we limit attention to studies that related to the whole population and compared the frequency of asthma in exposed and unexposed adults, whether using a prospective, case-control or cross-sectional design.

It is important to realize that there are difficulties in interpreting all the results from such studies strictly in terms of induction. In theory, induction relates to the probability of someone previously asthma-free getting the condition for the first time. Ideally, one would conduct a prospective study in which information is collected on onset of asthma in individuals who are asthma-free at the start of the study, and on regularly updated exposure information. Then one would base the analysis (using life-table methods) on data for each of a number of relatively short periods of time, which classified asthma-free subjects by exposure at the start of the period and compared the probability of onset of asthma in the different exposure groups. In principle one could also conduct a similar analysis using retrospective data on time of asthma onset and on history of exposure obtained in a case-control or cross-sectional study.

In practice, the data collected rarely conformed to this situation. Thus, of the 17 studies considered, there were six cross-sectional studies (JANSON, JEDRYC, MISHRA, NG[9], NHANE3, SAPALD) and two case-control studies (ORYSZC, PLATTS) for which the definition of asthma required the subject to have had symptoms currently or recently but which provided no information on time of onset of the asthmatic condition. Nor did they provide information on asthmatic subjects who were currently symptom-free. This lack of data means that one cannot interpret an association of ETS exposure with asthma as indicating a specific effect on either induction or exacerbation.

More insight might be gained from studies of whether the subject has ever had asthma. Assuming that asthma was not diagnosed at birth, which seems unlikely, the endpoint can be interpreted as induction between birth and current age. There were four cross-sectional studies (KRONQV, LARSS1, LARSS2, RAHERI) and one case-control study (PILOTT) where the definition of asthma was based on having ever had the condition. However, for none of these studies was time of onset of asthma considered and one could not therefore infer that the ETS exposure had occurred before the onset, particularly for study LARSS2 which related current ETS exposure to lifetime asthma. Three of these studies did relate childhood ETS exposure to lifetime asthma, study LARSS1 reporting a significant positive association (1.82, 1.28-2.58), study RAHERI reporting a significant negative association (0.30, 0.14-0.61), and study KRONQV merely reporting no significant relationship. However, even for this index, one cannot be sure whether the exposure was before or after the asthma.

There were in fact only four studies where the exposure occurred before asthma onset:

[9] Asthma was defined as "episodic wheeze and report of asthmatic symptoms diagnosed by a doctor as asthma during the past year" which might be taken to imply a new diagnosis in the last year, but which we have taken to imply the symptoms occurred in the last year but the asthma might have been longstanding.

- Study BECKE2, a prospective study in which serum cotinine was measured at baseline, provided two types of results. One, not relevant to asthma induction, related cotinine level to asthma prevalence at baseline. The other, which is relevant, related cotinine level to onset of asthma over the next 10 years, in those with no history of asthma at baseline. Here no association was seen, with the relative onset rate 0.96 (0.70-1.32) for those with cotinine 2-13 ng/ml as compared to those with cotinine <2 ng/ml.
- Study ROBBIN was also a prospective study, with onset after baseline, so childhood exposure was definitely before onset, and showed a non-significant positive relationship (1.57, 0.96-2.58). However, exposure was determined repeatedly during the follow-up period and it is not clear what was used to determine indices of adult exposure.
- Study JAAKK3 was a case-control study where the cases were first occurrences of asthma and previous asthma was also an exclusion for the controls. ETS exposure was determined in the last 12 months or on a lifetime basis, with a large number of indices of exposure studied. For total home and work exposure, an association was seen that was significant (1.97, 1.19-3.25) for most recent exposure, but not for earliest exposure (1.40, 0.99-1.96).
- Study THORN was a case-control study, nested within a cross-sectional study, involving cases with asthma first diagnosed in the previous 15 years. Questions were asked about ETS exposure and period of residence in the last six homes. To be classified as exposed, the case had to report exposure in the year of asthma diagnosis or the years previous to that year, with a comparable period of potential exposure considered for the controls. This study reported an association with household exposure, significant for males (4.80, 2.00-11.60) but not for females (1.50, 0.80-3.10).

While the data summarized above are suggestive of a possible association of ETS exposure with induction of asthma in adults, the relatively limited number of available studies and the somewhat heterogeneous nature of the results preclude a confident conclusion.

8.5. SUMMARY AND CONCLUSIONS

8.5.1. Methods Used to Collect and Analyse the Data and Scope of the Information Obtained

Based on papers published up to the end of 2004, epidemiological case-control, prospective and cross-sectional studies of prevalent or incident asthma in non-smoking adults have been identified. Only studies where the endpoint was “asthma” were included, and studies of “wheeze,” “wheezing bronchitis,” “chronic wheezing,” “asthma or wheeze” or “asthmatic bronchitis” were excluded.

Two linked databases were set up. One contains details of the characteristics of each study, while the other contains RR data relating to certain aspects of ETS exposure. For each study, the study database contains details of the study itself, the definition of asthma used,

and the potential confounding variables considered. For each of the RRs included, the RR database contains not only the RRs and 95% CIs, but precise details of their definition and information on how they were derived.

After examining over 400 papers, 16 principal studies were identified, plus one subsidiary study which was a subset of another study. Defined methods were used for entry and checking of data, and derivation of RRs.

One multicentre study was conducted in 17 countries, and the other studies were conducted in 10 countries. Only two studies started before 1988. 10 were of cross-sectional design, and all but two include both males and females. The largest study involved nearly 2500 asthma cases with a further four studies involving between 200 and 500 cases. Nine studies give results for lifetime or incident asthma, and nine studies for current (active) asthma. Data on total ETS exposure are available for seven studies, while data on household exposure are available for 13, and on workplace exposure for eight. Data on amount of passive smoke exposure are available for four studies. The potential non smoking confounding variables most commonly taken into account are age (13 studies), sex (9), location (8), education (5) and occupation (4).

Of the total of 117 RRs available, 115 relate to the principal studies. The number of RRs per principal study varies widely, from only one in three studies, to over 10 in three, the largest being a study with 48 RRs entered. 92 RRs are for sexes combined, and all relate to results for the full age range of the study and to all races within the study scope. 24 relate to lifetime asthma prevalence, 77 to current asthma prevalence and 16 to asthma incidence. 44 RRs relate to total ETS exposure, with 45 relating to household smoking and 28 to workplace exposure. 53 relate to current exposure, 7 to exposure as an adult and 12 to exposure as a child, with the remainder relating to lifetime or unspecified exposure. None relate to *in utero* exposure. 75 are adjusted for at least one variable. 13 have no RR value but only a statement of significance or non-significance. 86 of the RRs and CIs are as given originally or calculated directly from the numbers in the relevant 2×2 table. The rest involved more complex calculations.

8.5.2. Results

Results are presented of a series of meta-analyses aimed at giving insight into how the RR of asthma varies by the source, timing and amount of ETS exposure, the definition of the asthma outcome, the sex and age of the subject, the location, timing, size and type of study, the source of the information on exposure and diagnosis, and the extent of adjustment for confounding variables.

The main conclusions reached from the analyses are as follows:

There is an association between ETS exposure and asthma in adults. Including results for non-smokers as well as for never smokers, and giving preference to exposure estimates as early in life as available and to results for lifetime rather than current asthma, meta-analysis RR estimates (95% CI) for total ETS exposure (or nearest equivalent), based on 18 independent results, are 1.14 (1.06-1.23) using the fixed effects model and 1.19 (1.04-1.35) using the random effects model. Corresponding meta-analysis estimates for household exposure (n = 14) are 1.13 (1.04-1.23) fixed effects and 1.16 (1.00-1.35) random effects. For workplace exposure (n = 6), they are 1.37 (1.18-1.59) fixed effects and 1.36 (1.09-1.70)

random effects. Restricting results to those for never smokers, giving preference to most recent exposure estimates or giving preference to current rather than lifetime asthma affects the conclusions little, the meta-analyses generally being consistent with a weak, but statistically significant, association, with risk about 20% higher in the ETS-exposed group. (However, some of the similarity in the various alternative analyses arises because some studies only provide limited estimates, e.g. for a single timing of exposure or a single definition of asthma.) Meta-analyses for childhood ETS exposure are also consistent with about a 20% increased risk, but are not clearly statistically significant (1.27, 1.04-1.54 fixed effects; 1.26 , 0.88-1.81 random effects), being based on only four estimates.

Data on dose-response are rather limited, with only four studies providing estimates by level of exposure, an additional two studies providing results of trend analyses. However, the overall results are consistent with a significantly increased risk in the highest exposure group, a conclusion which is independent of the sources and measures of ETS exposure considered.

There is evidence of significant heterogeneity between estimates in virtually all the meta-analyses conducted. Investigation of heterogeneity is limited by the small number of studies considered, and by the fact that one large study has a very large weight and that individual studies have unusually high or low RR estimates for reasons that are not clear. Although there is evidence that associations are stronger in European studies than in studies conducted elsewhere, in case-control than in prospective studies, and in smaller than in larger studies, the extent to which these observed significant variations represent independent or meaningful differences is unclear.

There is a tendency for smaller studies to provide larger RR estimates, but formal testing of publication bias using Egger's method does not show any significant evidence of it. Although it is possible that some publication bias may exist, the fact that 15 of the 18 estimates included in the total exposure meta-analysis cited above are greater than 1.0 makes it unlikely that publication bias could explain the whole association.

There is no direct evidence that diagnostic bias, lack of representativeness or misclassification of exposure are important issues in the interpretation of the results. However, the data available to investigate this are limited. Nor is there any evidence that our decision to include estimates for non-smokers (i.e. including former smokers) in our analyses materially affected the findings. We preferred to exclude estimates for the whole population (i.e. including current smokers) because of reports that smoking caused asthma.

There is no clear evidence of confounding by a variety of non-smoking lifestyle factors, although a number of different approaches were used to investigate this. Although most studies took into account potential confounders, some factors that might be considered important were only rarely taken account of (e.g. pets only in one study, and diet, exercise and exposure to infections in none).

8.5.3. Other Reviews

The 1993 EPA report on respiratory health effects of passive smoking (National Cancer Institute, 1993) included a chapter on *"Respiratory disorders other than cancer."* However, the section on *"Asthma"* only considered data for children, while the section on *"Respiratory symptoms and lung function in adults"* did not consider asthma.

The next year, members of IARC published a review paper (Trédaniel et al., 1994) entitled *"Exposure to environmental tobacco smoke and adult non-neoplastic respiratory diseases."* This considered that *"no definite conclusion (excluding the acute irritating effect of ETS on respiratory mucous membranes) can be drawn"* although there was *"a need for further epidemiological studies."* The section on *"Asthma"* was mainly concerned with possible exacerbating and allergenic effects of ETS, citing a number of experimental studies, and did not consider any epidemiological evidence linking asthma onset or prevalence to ETS.

Later that year, the results of study SAPALD were published and an associated editorial entitled *"Passive smoking and adults: new evidence for adverse events"* (Leaderer & Samet, 1994) summarized its findings and also cited results from ROBBIN and of a study (Dayal et al., 1994) for which the endpoint was obstructive airway disease and not asthma. The authors argued that the new studies *"suggest a need for reconsideration of the evidence on passive smoking and respiratory symptoms and illnesses in adults."*

A later review was entitled *"Effects of environmental tobacco smoke exposure on pulmonary function and respiratory health in adults: update 1997"* (Witorsch, 1998). This contained quite a detailed analysis of the experimental evidence on ETS exposure in asthmatics. As regards epidemiology, no actual attempt was made to separate out effects on asthmatics and the normal population and of the 18 studies cited of *"asthma incidence, exacerbation or symptoms,"* the only data cited that are relevant to this report relate to studies JEDRYC, NG, ROBBIN and SAPALD. Witorsch regarded the evidence from the 18 studies as inconsistent, though did not present any quantitative overview.

The same year, a review was entitled *"Passive smoking and risk of adult asthma and COPD: an update"* (Coultas, 1998). Results related to asthma onset (rather than exacerbation) were cited from three studies, two considered by us (ROBBIN, SAPALD) and one from a study (Hu et al., 1997) unrestricted to non-smokers. Coultas concluded that *"While growing evidence suggests that passive smoking is a risk factor for adult onset asthma and COPD, the magnitude of the associations is small. However additional evidence on the relationship between passive smoking and asthma and COPD is needed to fulfil the criteria for causality, particularly the criteria of temporality and dose-response."*

The next year, the California EPA published their overview entitled *"Health effects of exposure to environmental tobacco smoke"* (National Cancer Institute, 1999). In section 6.2.4, they reviewed evidence on *"Chronic pulmonary disease and respiratory symptoms (adults)."* Most of the studies reviewed were not relevant to this report, but data were summarized from studies NG, ROBBIN and SAPALD (though not from studies JEDRYC or PLATTS which had been reported well before this report). Later in the report, in section 6.4, the California EPA conclude that *"There is consistent and compelling evidence that ETS is a risk factor for induction of new cases of asthma."* However, this conclusion seems to have been based mainly on the findings for children, discussed in chapter 9, as no conclusions regarding asthma induction in adults are made, other than to note (in section 6.2.4) that *"The results of Leuenberger et al. (1994), Robbins et al. (1993) and other recent papers, however, suggest that ETS exposure may make a significant contribution to chronic respiratory symptoms in adults."*

In the same year, a short review was published on *"Environmental tobacco smoke exposure and asthma in adults"* (Weiss et al., 1999). In the section *"The role of ETS in causing asthma in adults,"* results were reviewed from studies we considered (ROBBIN,

SAPALD) and from studies we rejected (Flodin et al., 1995; Hu et al., 1997) as not being restricted to non-smokers. The authors concluded: *"These studies have differing designs – cross-sectional, cohort, and case-control – but their findings provide an indication of potential effects of ETS exposure in the workplace on persons with asthma. Their results may be subject to the complex biases considered above – both selection bias and both differential and nondifferential misclassification of exposure. They highlight the difficulty and challenge of accurately assessing workplace exposure and of interpreting findings that may be subject to selection bias that cannot be characterized readily. In summary, at present there are limited epidemiologic data on the relationship of ETS exposure as a cause of adult asthma."*

A longer review entitled *"Environmental tobacco smoke and adult asthma"* (Eisner & Blanc, 2000) concluded that *"The evidence indicates that adults who are exposed to ETS have a greater risk of developing asthma."* The studies cited in the relevant table (6.1) only extend by one those considered in the previous review (Weiss et al., 1999), including additionally the study (Dayal et al., 1994) for which the endpoint was obstructive airway disease. Although section 6.8 *"ETS exposure and adult asthma: evidence for a causal association"* discusses issues such as confounding, biased report of exposure, and dose-response, there is no discussion of the problems of separating out potential effects of ETS exposure on induction and exacerbation. The limited number of relevant studies was also not really put over, especially when one restricts attention specifically to induction of asthma in non-smokers.

Another review published in the same year, on *"Environmental tobacco smoke and respiratory diseases"* (Jaakkola, 2000) was broad ranging. In the section on adults, a subsection deals with *"Induction of asthma."* Five studies are cited; three we consider (NG, ROBBIN, SAPALD) and two (Flodin et al., 1995; Hu et al., 1997) which were not of non-smokers. Jaakkola concludes that *"These findings provide evidence that ETS causes asthma in adulthood, but more studies, especially with a longitudinal design, are needed before making any definite conclusions."* A further review by the same author in 2002 (Jaakkola & Jaakkola, 2002) added study JAAKK3 and presented effectively unchanged conclusions.

A brief editorial the following year (Bousquet & Vignola, 2001) was entitled *"Exposure to environmental tobacco smoke and asthma."* It stated that there were *"only five studies examining exposure to ETS and adult onset asthma,"* three of which related to studies considered by us (ROBBIN, SAPALD, THORN) with two (Flodin et al., 1995; Hu et al., 1997) not of non-smokers. The authors concluded that *"In these studies, some methodological barriers mostly inherent in the study design limited the available data and the evaluation of the adequacy of the data for risk assessment. Thus, more epidemiologic studies are needed to confirm the causative role of ETS in asthma."*

A further review by Eisner entitled *"Environmental tobacco smoke and adult asthma"* (Eisner, 2002a) included a section *"Environmental tobacco smoke and new-onset adult asthma"* which considered data from far more studies than he considered in 2000. Data from seven of the studies we considered are included (KRONQV, JANSON, LARSS1, NG, ROBBIN, SAPALD, THORN) as well as from studies we have rejected, three (Dayal et al., 1994; Flodin et al., 1995; Hu et al., 1997) for reasons noted above and one (Iribarren et al., 2001) because the outcome was hay fever or asthma not asthma. It should be noted that, although the title of the section refers to *"new-onset"* adult asthma, some of the studies (e.g. JANSON, NG, SAPALD) only required cases to have recent occurrences, so the asthma could have started years earlier and is not necessarily *"new-onset"* at all. As with the previous

review (Eisner & Blanc, 2000), the discussion considers induction and exacerbation together, without looking at the difficulties of disentangling the two. Nevertheless, he concluded that *"the evidence suggests a causal relationship between ETS exposure and new-onset asthma."*

In 2004, a short but wide-ranging review on *"The effect of passive smoking on respiratory health in children and adults"* was published (Janson, 2004). Only one paragraph concerned asthma in adults, reporting the associations seen in the studies LARSS2, ROBBIN, SAPALD and THORN. There was no discussion of any potential bias or of separating potential effects of ETS on induction and exacerbation. The review concluded that *"Passive smoking is a widespread, important and avoidable risk factor for respiratory symptoms in both children and adults."*

In their *"Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant"* (California Environmental Protection Agency, 2005), the California EPA include *"asthma induction and exacerbation in children and adults"* in a list of *"Effects Causally Associated with ETS Exposure."* They noted that in their earlier report (National Cancer Institute, 1999), they had reviewed five studies that supported an association between ETS exposure and adult asthma. In one of these (Dayal et al., 1994) the endpoint was obstructive airway disease, not asthma, and two (Greer et al., 1993; Robbins et al., 1993) related to the same study, so that only three relevant studies (NG, ROBBIN, SAPALD) were actually considered. Table 6.51, *"ETS and new-onset asthma in adolescents and adults,"* gives the relevant data for the additional studies in section 6.5.2.1. Based on this table, one can determine that, of the 15 papers cited there, four are not of non-smokers (Flodin et al., 1995; Hu et al., 1997; Radon et al., 2002; Eagan et al., 2004), two are not of asthma (Iribarren et al., 2001; Upton et al., 2004) and two (Greer et al., 1993; McDonnell et al., 1999) are (as recognized by the authors) reports from the same study they had considered earlier (ROBBIN). The other seven references relate to six studies we consider (JAAKK3, JANSON, KRONQV, LARSS1, PILOTT, THORN), two references (Janson et al., 2001; Svanes et al., 2004) being to the same study. Despite the title of their table, three of these studies (KRONQV, JANSON, LARSS1) do not actually relate to *"new-onset"* asthma, as is true also for two of the three of our selected studies they considered in their previous report (NG, SAPALD). Overall, the report includes only 8 of the 17 studies we consider relevant.

The report does not contain any section giving an overall meta-analysis or interpretation of the data specifically on asthma induction in adults, section 6.5.2.1 merely giving a description of each of the studies they consider relevant published since the previous report. The next section, 6.5.2.2, is headed *"Conclusions – Asthma Induction in Adolescents and Adults."* The authors point out that most studies *"examined at least some potential confounders"* with the association *"probably not explained by confounding"* and refer to the possibilities of exposure bias. They note the existence of dose-response relationships, as we find (see Table 8.12), but argue unreasonably (see §8.4.11) that *"the temporal relationship between ETS and the development of asthma or asthma-like symptoms was clearly delineated in most studies."* They note that *"a key issue is distinguishing the development of incident adult-onset asthma, as opposed to exacerbation of previously established disease,"* citing in support one study not of non-smokers (Hu et al., 1997) and three we consider as most relevant in §8.4.11 (JAAKK3, ROBBIN, THORN), though failing to cite the fourth relevant study (BECKE2) which finds no association.

The report concludes that *"In sum, studies of ETS and adult-onset asthma have controlled for bias and confounding. They have demonstrated temporality, exposure-response*

relationship, consistency, coherence, and biologic plausibility, supporting a causal relationship." This clearly overstates the evidence from a rather limited database.

8.5.4. Conclusions

There is an association between ETS exposure and asthma in adults and some evidence of a dose-response relationship. While the data are consistent with ETS exposure inducing asthma in adults, they do not clearly demonstrate a cause and effect relationship. Limitations of the evidence include the relatively small number of studies (particularly those that specifically relate to induction), the lack of consideration of *in utero* exposure and the lack of control for relevant confounding variables.

8.6. REFERENCES

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Table A1. Adults - Meta-analysis of Biochemical/Total/Household/Workplace Exposure (preferring earliest), Lifetime/Current Asthma

This analysis is restricted to results for:
1) Biochemical, total, household (overall), parental, or workplace exposure
2) Results not by amount of exposure
3) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
4) ASTHMA : lifetime, current
5) EXPOS : biochemical (cotinine), total, household, workplace
6) WHESMO : 3=childhood, 1=lifetime, 10=adult, 7=recent, 6=unspec, 2=current
7) WHOHOU : household overall, mother
8) UNEXTI : unexposed group never, non (i.e. not at time defined for exposed group)
9) For overlapping studies: principal rather than subsidiary studies
Finally for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	18
NS	14
Wt	671.57
Het Chi	37.20
Het df	17
Het P	**
Fixed RR	1.14
RRl	1.06
RRu	1.23
P	+++
Random RR	1.19
RRl	1.04
RRu	1.35
P	+
Asymm P	N.S.

	Sex			*Asthma definition*		*Study type*			*Start year of study*			*Publication year*	
	both	male	female	lifetime	current	CC	Pr	CS	<1990	1990-99	unknown	1990-99	2000+
N	10	3	5	9	9	5	3	10	4	10	4	5	13
Het P	*	*	N.S.	***	N.S.	N.S.	*	N.S.	(*)	*	N.S.	N.S.	**
Fixed RR	1.17	1.28	1.05	1.20	1.12	1.56	0.93	1.15	0.99	1.21	0.89	1.26	1.13
RRl	1.05	1.06	0.92	1.06	1.02	1.19	0.76	1.06	0.84	1.11	0.57	1.02	1.04
RRu	1.30	1.55	1.20	1.36	1.22	2.05	1.13	1.26	1.16	1.32	1.40	1.55	1.22
P	++	++	N.S.	++	+	++	N.S.	++	N.S.	+++	N.S.	+	++
Between P	N.S.			N.S.		**			(*)			N.S.	

	Continent			*Ex smokers*		*Exposure*				*Exposed group : when exposed*				
	NAmer	Europe	Oth/Mult	excluded	included	Hh	Hh,Wk	Cot	Work	life	adult	child	current	unspec
N	4	9	5	13	5	11	4	2	1	2	2	2	11	1
Het P	(*)	*	N.S.	*	(*)	*	N.S.	N.S.	N.S.	N.S.	*	N.S.	N.S.	N.S.
Fixed RR	0.99	1.40	1.11	1.20	1.00	1.16	1.34	0.84	1.13	1.36	2.31	1.73	1.07	1.09
RRl	0.84	1.21	1.00	1.10	0.86	1.05	1.13	0.67	0.80	1.00	1.35	1.30	0.99	0.65
RRu	1.16	1.63	1.23	1.31	1.16	1.27	1.59	1.04	1.59	1.85	3.96	2.31	1.17	1.82
P	N.S.	+++	(+)	+++	N.S.	++	+++	N.S.	N.S.	(+)	++	+++	(+)	N.S.
Between P	**			*		*				**				

	Lowest age in RR			*Highest age in RR*			*Physician diagnosis*		*Analysis type*		*Number of cases*			
	15-19	20-25	60+	-55	60-69	70+	yes	no/mixed	prevlnce	onset	1-100	101-400	401+	unknown
N	7	8	3	7	4	7	11	7	15	3	7	3	5	3
Het P	**	N.S.	N.S.	**	N.S.	N.S.	***	N.S.	**	N.S.	*	N.S.	N.S.	N.S.
Fixed RR	1.12	1.38	1.08	1.02	1.41	1.10	1.17	1.12	1.13	1.21	1.40	1.50	1.05	1.13
RRl	0.99	1.15	0.97	0.86	1.20	1.00	1.05	1.01	1.05	0.98	1.05	1.25	0.95	0.92
RRu	1.27	1.66	1.21	1.20	1.66	1.22	1.31	1.24	1.23	1.49	1.86	1.81	1.15	1.40
P	(+)	+++	N.S.	N.S.	+++	+	++	+	++	(+)	+	+++	N.S.	N.S.
Between P	(*)			*			N.S.		N.S.		**			

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	9	9	15	3	3	15	10	8	2	16	3	15	3	15
Het P	**	*	***	N.S.	N.S.	*	N.S.	**	N.S.	**	N.S.	**	N.S.	**
Fixed RR	1.18	1.12	1.15	1.11	0.86	1.19	1.09	1.35	1.10	1.18	1.31	1.11	1.11	1.18
RRl	1.05	1.01	1.06	0.86	0.70	1.10	1.00	1.15	0.98	1.07	1.09	1.03	0.99	1.06
RRu	1.32	1.24	1.24	1.42	1.06	1.30	1.19	1.58	1.23	1.30	1.58	1.21	1.23	1.31
P	++	+	+++	N.S.	N.S.	+++	+	+++	N.S.	++	++	+	(+)	++
Between P	N.S.		N.S.		**		*		N.S.		N.S.		N.S.	

	Study adjusts for cooking, heating		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for subject's medical history*		*Study adjusts for ex smoking or other ETS exposure*		*Number of adjustment variables*				
	Yes	No	Yes	No	Yes	No	Yes	No	0	2	3-5	6-9	10+
N	4	14	4	14	5	13	4	14	3	2	7	4	2
Het P	N.S.	**	N.S.	**	(*)	*	N.S.	**	N.S.	*	**	N.S.	N.S.
Fixed RR	1.09	1.20	1.13	1.16	1.41	1.10	1.26	1.12	1.11	2.31	1.07	1.30	1.10
RRl	0.97	1.08	1.01	1.04	1.17	1.01	1.05	1.03	0.86	1.35	0.93	1.09	0.98
RRu	1.21	1.32	1.26	1.29	1.69	1.19	1.51	1.22	1.42	3.96	1.24	1.55	1.23
P	N.S.	+++	+	++	+++	+	+	++	N.S.	++	N.S.	++	N.S.
Between P	N.S.		N.S.		*		N.S.		*				

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for ex smoking or other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*		
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	Sum/F&L
N	9	9	15	3	3	15	15	3	11	3	4
Het P	**	*	***	N.S.	N.S.	**	***	N.S.	***	N.S.	N.S.
Fixed RR	1.18	1.12	1.15	1.11	1.21	1.13	1.15	1.11	1.12	1.11	1.30
RRl	1.05	1.01	1.06	0.86	0.98	1.05	1.06	0.86	1.03	0.86	1.06
RRu	1.32	1.24	1.24	1.42	1.49	1.23	1.24	1.42	1.22	1.42	1.60
P	++	+	+++	N.S.	(+)	++	+++	N.S.	++	N.S.	+
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		

Table A2. Adults - Meta-analysis of Biochemical/Total/Household/Workplace (preferring earliest) - Ex-smokers excluded, Lifetime/Current Asthma

This analysis is restricted to results for:
1) Biochemical, total, household (overall), parental, or workplace exposure
2) Ex-smokers excluded
3) Results not by amount of exposure
4) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
5) ASTHMA : lifetime, current
6) EXPOS : biochemical (cotinine), total, household, workplace
7) WHESMO : 3=childhood, 1=lifetime, 10=adult, 7=recent, 6=unspec, 2=current
8) WHOHOU : household overall, mother
9) UNEXTI : unexposed group never, non (i.e. not at time defined for exposed group)
10) For overlapping studies: principal rather than subsidiary studies
Finally for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	13
NS	10
Wt	503.93
Het Chi	25.13
Het df	12
Het P	*
Fixed RR	1.20
RRl	1.10
RRu	1.31
P	+++
Random RR	1.27
RRl	1.09
RRu	1.49
P	++
Asymm P	N.S.

	Sex			*Asthma definition*		*Study type*			*Start year of study*			*Continent*		
	both	male	female	lifetime	current	CC	Pr	CS	<1990	1990-99	unknown	NAmer	Europe	Oth/Mult
N	5	3	5	5	8	5	0	8	0	9	4	0	9	4
Het P	N.S.	*	N.S.	*	N.S.	N.S.		(*)		**	N.S.		*	N.S.
Fixed RR	1.35	1.28	1.05	1.49	1.12	1.56		1.16		1.21	0.89		1.40	1.11
RRl	1.17	1.06	0.92	1.25	1.01	1.19		1.06		1.11	0.57		1.21	1.00
RRu	1.56	1.55	1.20	1.78	1.23	2.05		1.27		1.32	1.40		1.63	1.23
P	+++	++	N.S.	+++	+	++		++		+++	N.S.		+++	(+)
Between P	*			**		*			N.S.			*		

Table A3. Adults - Meta-analysis of Biochemical/Total/Household/Workplace Exposure (preferring most recent), Lifetime/Current Asthma

This analysis is restricted to results for:
1) Biochemical, total, household (overall), parental, or workplace exposure
2) Results not by amount of exposure
3) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
4) ASTHMA : lifetime, current
5) EXPOS : biochemical (cotinine), total, household, workplace
6) WHESMO : 2=current, 7=recent, 6=unspec, 10=adult, 1=lifetime, 3=childhood
7) WHOHOU : household overall, mother
8) UNEXTI : unexposed group never, non (i.e. not at time defined for exposed group)
9) For overlapping studies: principal rather than subsidiary studies
Finally for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	18
NS	14
Wt	655.68
Het Chi	42.09
Het df	17
Het P	***
Fixed RR	1.15
RRl	1.07
RRu	1.24
P	+++
Random RR	1.21
RRl	1.05
RRu	1.40
P	++
Asymm P	N.S.

Table A4. Adults - Meta-analysis of Total/Household/Workplace Exposure in Childhood, Lifetime/Current Asthma

This analysis is restricted to results for:
1) Total, household (overall), parental, or workplace exposure
2) Childhood exposure
3) Results not by amount of exposure
4) Results complete enough for use in metaanalysis
Within each study, results are then selected (in the following order of preference, within each sex) for:
5) ASTHMA : lifetime, current
6) EXPOS : biochemical (cotinine), total, household, workplace
7) WHOHOU : household overall, mother
8) UNEXTI : unexposed group never, non (i.e. not at time defined for exposed group)
9) For overlapping studies: principal rather than subsidiary studies
Finally for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	4
NS	3
Wt	102.26
Het Chi	10.01
Het df	3
Het P	*
Fixed RR	1.27
RRl	1.04
RRu	1.54
P	+
Random RR	1.26
RRl	0.88
RRu	1.81
P	N.S.
Asymm P	N.S.

	Sex			*Asthma definition*		*Study type*			*Start year of study*		
	both	male	female	lifetime	current	CC	Pr	CS	<1990	1990-99	unknown
N	2	1	1	2	2	0	1	3	1	3	0
Het P	N.S.	N.S.	N.S.	N.S.	N.S.		N.S.	*	N.S.	*	
Fixed RR	1.73	0.81	1.10	1.73	0.97		1.57	1.22	1.57	1.22	
RRl	1.30	0.54	0.78	1.30	0.75		0.96	0.99	0.96	0.99	
RRu	2.31	1.22	1.55	2.31	1.26		2.57	1.50	2.57	1.50	
P	+++	N.S.	N.S.	+++	N.S.		(+)	(+)	(+)	(+)	
Between P	**			**		N.S.			N.S.		

	Continent			*Ex smokers*	
	NAmer	Europe	Oth/Mult	excluded	included
N	1	1	2	3	1
Het P	N.S.	N.S.	N.S.	*	N.S.
Fixed RR	1.57	1.82	0.97	1.22	1.57
RRl	0.96	1.28	0.75	0.99	0.96
RRu	2.57	2.58	1.26	1.50	2.57
P	(+)	+++	N.S.	(+)	(+)
Between P	*			N.S.	

Table A5. Adults - Meta-analysis of Total/Household/Workplace Exposure in Childhood (preferring father), Lifetime/Current Asthma

This analysis is restricted to results for:
1) Total, household (overall), parental, or workplace exposure
2) Childhood exposure
3) Results not by amount of exposure
4) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
5) ASTHMA : lifetime, current
6) EXPOS : biochemical (cotinine), total, household, workplace
7) WHOHOU : household overall, father
8) UNEXTI : unexposed group never, non (i.e. not at time defined for exposed group)
9) For overlapping studies: principal rather than subsidiary studies
Finally for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	4
NS	3
Wt	117.90
Het Chi	19.78
Het df	3
Het P	***
Fixed RR	1.11
RRl	0.93
RRu	1.33
P	N.S.
Random RR	1.18
RRl	0.74
RRu	1.90
P	N.S.
Asymm P	N.S.

Table A6. Adults - Meta-analysis of Biochemical/Total/Household/Workplace (preferring earliest, and preferring current asthma), Current/Lifetime Asthma

This analysis is restricted to results for:
1) Biochemical, total, household (overall), parental, or workplace exposure
2) Results not by amount of exposure
3) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
4) ASTHMA : current, lifetime
5) EXPOS : biochemical (cotinine), total, household, workplace
6) WHESMO : 3=childhood, 1=lifetime, 10=adult, 7=recent, 6=unspec, 2=current
7) WHOHOU : household overall, mother
8) UNEXTI : unexposed group never, non (i.e. not at time defined for exposed group)
9) For overlapping studies: principal rather than subsidiary studies
Finally for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	18
NS	14
Wt	652.19
Het Chi	38.63
Het df	17
Het P	**
Fixed RR	1.14
RRl	1.06
RRu	1.24
P	+++
Random RR	1.20
RRl	1.04
RRu	1.37
P	++
Asymm P	N.S.

Table A7. Adults - Meta-analysis of Household exposure (preferring earliest), Lifetime/Current Asthma

This analysis is restricted to results for:
1) Household (overall) or parental exposure
2) Results not by amount of exposure
3) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
4) ASTHMA : lifetime, current
5) WHESMO : 3=childhood, 1=lifetime, 10=adult, 7=recent, 6=unspec, 2=current
6) WHOHOU : household overall, mother
7) UNEXTI : unexposed group never, non (i.e. not at time defined for exposed group)
8) For overlapping studies: principal rather than subsidiary studies
Finally for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	14
NS	10
Wt	513.05
Het Chi	25.99
Het df	13
Het P	*
Fixed RR	1.13
RRl	1.04
RRu	1.23
P	++
Random RR	1.16
RRl	1.00
RRu	1.35
P	+
Asymm P	N.S.

	Sex			*Asthma definition*		*Study type*			*Start year of study*		
	both	male	female	lifetime	current	CC	Pr	CS	<1990	1990-99	unknown
N	4	4	6	4	10	5	0	9	1	9	4
Het P	N.S.	**	N.S.	*	N.S.	*		(*)	N.S.	**	N.S.
Fixed RR	1.24	1.18	1.05	1.69	1.07	1.33		1.11	1.11	1.15	0.89
RRl	1.04	1.00	0.93	1.31	0.98	1.01		1.01	0.85	1.04	0.57
RRu	1.46	1.41	1.19	2.19	1.18	1.75		1.22	1.44	1.26	1.40
P	+	(+)	N.S.	+++	N.S.	+		+	N.S.	++	N.S.
Between P	N.S.			***		N.S.			N.S.		

	Continent			*Ex smokers*	
	NAmer	Europe	Oth/Mult	excluded	included
N	1	7	6	12	2
Het P	N.S.	**	N.S.	**	N.S.
Fixed RR	1.11	1.39	1.08	1.14	1.10
RRl	0.85	1.13	0.98	1.04	0.87
RRu	1.44	1.71	1.20	1.25	1.39
P	N.S.	++	N.S.	++	N.S.
Between P	(*)			N.S.	

Table A8. Adults - Meta-analysis of Household exposure (preferring most recent), Lifetime/Current Asthma

This analysis is restricted to results for:
1) Household (overall) or parental exposure
2) Results not by amount of exposure
3) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
4) ASTHMA : lifetime, current
5) WHESMO : 2=current, 7=recent, 6=unspec, 10=adult, 1=lifetime, 3=childhood
6) WHOHOU : household overall, mother
7) UNEXTI : unexposed group never, non (i.e. not at time defined for exposed group)
8) For overlapping studies: principal rather than subsidiary studies
Finally for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	13
NS	10
Wt	441.99
Het Chi	27.62
Het df	12
Het P	**
Fixed RR	1.17
RRl	1.06
RRu	1.28
P	++
Random RR	1.26
RRl	1.05
RRu	1.53
P	+
Asymm P	N.S.

Table A9. Adults - Meta-analysis of Workplace Exposure (preferring earliest), Lifetime/Current Asthma

This analysis is restricted to results for:
1) Workplace exposure
2) Results not by amount of exposure
3) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
4) ASTHMA : lifetime, current
5) WHESMO : 3=childhood, 1=lifetime, 10=adult, 7=recent, 6=unspec, 2=current
6) WHOHOU : household overall, mother
7) UNEXTI : unexposed group never, non (i.e. not at time defined for exposed group)
8) For overlapping studies: principal rather than subsidiary studies
Finally for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	6
NS	5
Wt	166.38
Het Chi	7.97
Het df	5
Het P	N.S.
Fixed RR	1.37
RRl	1.18
RRu	1.59
P	+++
Random RR	1.36
RRl	1.09
RRu	1.70
P	++
Asymm P	N.S.

	Sex			*Asthma definition*		*Study type*			*Start year of study*		
	both	male	female	lifetime	current	CC	Pr	CS	<1990	1990-99	unknown
N	4	1	1	1	5	3	0	3	1	3	2
Het P	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.		N.S.	N.S.	N.S.	N.S.
Fixed RR	1.40	0.79	0.43	1.13	1.44	1.34		1.38	1.36	1.44	0.55
RRl	1.20	0.17	0.13	0.80	1.21	0.95		1.16	1.10	1.16	0.21
RRu	1.64	3.59	1.45	1.59	1.70	1.91		1.63	1.70	1.79	1.41
P	+++	N.S.	N.S.	N.S.	+++	(+)		+++	++	+++	N.S.
Between P	N.S.			N.S.		N.S.			N.S.		

	Continent			*Ex smokers*	
	NAmer	Europe	Oth/Mult	excluded	included
N	1	4	1	5	1
Het P	N.S.	N.S.	N.S.	(*)	N.S.
Fixed RR	1.36	1.23	1.90	1.38	1.36
RRl	1.10	0.96	1.25	1.11	1.10
RRu	1.70	1.57	2.88	1.70	1.70
P	++	(+)	++	++	++
Between P	N.S.			N.S.	

Table A10. Adults - Meta-analysis of Workplace Exposure (preferring most recent), Lifetime/Current Asthma

This analysis is restricted to results for:
1) Workplace exposure
2) Results not by amount of exposure
3) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
4) ASTHMA : lifetime, current
5) WHESMO : 2=current, 7=recent, 6=unspec, 10=adult, 1=lifetime, 3=childhood
6) UNEXTI : unexposed group never, non (i.e. not at time defined for exposed group)
7) For overlapping studies: principal rather than subsidiary studies
Finally for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	6
NS	5
Wt	152.36
Het Chi	10.23
Het df	5
Het P	(*)
Fixed RR	1.39
RRl	1.19
RRu	1.63
P	+++
Random RR	1.40
RRl	1.06
RRu	1.85
P	+
Asymm P	N.S.

Tables B1, B2. Adults - Meta-analysis of Total/Household/Workplace Exposure : Low/High Dose, Lifetime/Current Asthma, (preferring number of cigarettes)

These analyses are restricted to results for:
1) Total, household (overall) or workplace exposure
2) Results for low amount of exposure (B1) or for high amount of exposure (B2)
3) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
4) ASTHMA : lifetime, current
5) EXPOS : total, household, workplace
6) MEAS : number of cigarettes, hours per day (0 indicates <1)
7) For overlapping studies: principal rather than subsidiary studies
Finally for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

	Table B1 *Low Dose*	Table B2 *High Dose*
N	4	4
NS	4	4
Wt	62.70	39.90
Het Chi	4.96	0.96
Het df	3	3
Het P	N.S.	N.S.
Fixed RR	1.03	1.63
RRl	0.80	1.19
RRu	1.32	2.22
P	N.S.	++
Random RR	1.07	1.63
RRl	0.75	1.19
RRu	1.51	2.22
P	N.S.	++
Asymm P	N.S.	N.S.

Tables B3, B4. Adults - Meta-analysis of Household Exposure : Low/High Dose, Lifetime/Current Asthma, (preferring number of cigarettes)

These analyses are restricted to results for:
1) Household (overall) exposure
2) Results for low amount of exposure (B3) or for high amount of exposure (B4)
3) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
4) ASTHMA : lifetime, current
5) MEAS : number of cigarettes, hours per day
6) For overlapping studies: principal rather than subsidiary studies
Finally for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

	Table B3	Table B4
	Low Dose	*High Dose*
N	2	2
NS	2	2
Wt	5.90	6.71
Het Chi	2.60	0.59
Het df	1	1
Het P	N.S.	N.S.
Fixed RR	1.27	1.39
RRl	0.57	0.65
RRu	2.85	2.96
P	N.S.	N.S.
Random RR	1.59	1.39
RRl	0.37	0.65
RRu	6.88	2.96
P	N.S.	N.S.
Asymm P		

Tables B5, B6. Adults - Meta-analysis of Workplace Exposure : Low/High Dose, Lifetime/Current Asthma, (preferring number of cigarettes)

These analyses are restricted to results for:
1) Workplace exposure
2) Results for low amount of exposure (B5) or for high amount of exposure (B6)
3) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
4) ASTHMA : lifetime, current
5) MEAS : number of cigarettes, hours per day (0 indicates <1)
6) For overlapping studies: principal rather than subsidiary studies
Finally for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

	Table B5	Table B6
	Low Dose	*High Dose*
N	2	2
NS	2	2
Wt	25.40	16.45
Het Chi	3.90	0.75
Het df	1	1
Het P	*	N.S.
Fixed RR	1.08	2.04
RRl	0.73	1.26
RRu	1.59	3.31
P	N.S.	++
Random RR	1.26	2.04
RRl	0.53	1.26
RRu	2.97	3.31
P	N.S.	++
Asymm P		

Tables B7, B8. Adults - Meta-analysis of Total/Household/Workplace Exposure : Low/High Dose, Lifetime/Current Asthma, (preferring pack-years)

These analyses are restricted to results for:
1) Total, household (overall) or workplace exposure
2) Results for low amount of exposure (B7) or for high amount of exposure (B8)
3) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
4) ASTHMA : lifetime, current
5) EXPOS : total, household, workplace
6) MEAS : pack-years, number of cigarettes, hours per day (0 indicates <1)
7) For overlapping studies: principal rather than subsidiary studies
Finally for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

	Table B7 *Low Dose*	Table B8 *High Dose*
N	4	4
NS	4	4
Wt	69.14	55.91
Het Chi	0.56	0.83
Het df	3	3
Het P	N.S.	N.S.
Fixed RR	0.90	1.66
RRl	0.71	1.28
RRu	1.14	2.16
P	N.S.	+++
Random RR	0.90	1.66
RRl	0.71	1.28
RRu	1.14	2.16
P	N.S.	+++
Asymm P	N.S.	N.S.

Tables B9, B10. Adults - Meta-analysis of Household Exposure : Low/High Dose, Lifetime/Current Asthma, (preferring pack-years)

These analyses are restricted to results for:
1) Household (overall) exposure
2) Results for low amount of exposure (B9) or for high amount of exposure (B10)
3) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
4) ASTHMA : lifetime, current
5) MEAS : pack-years, number of cigarettes, hours per day
6) For overlapping studies: principal rather than subsidiary studies
Finally for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

	Table B9	Table B10
	Low Dose	*High Dose*
N	2	2
NS	2	2
Wt	17.26	24.03
Het Chi	0.03	0.10
Het df	1	1
Het P	N.S.	N.S.
Fixed RR	0.93	1.42
RRl	0.58	0.95
RRu	1.48	2.12
P	N.S.	(+)
Random RR	0.93	1.42
RRl	0.58	0.95
RRu	1.48	2.12
P	N.S.	(+)
Asymm P		

Tables B11, B12. Adults - Meta-analysis of Workplace Exposure : Low/High Dose, Lifetime/Current Asthma, (preferring pack-years)

These analyses are restricted to results for:
1) Workplace exposure
2) Results for low amount of exposure (B11) or for high amount of exposure (B12)
3) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
4) ASTHMA : lifetime, current
5) MEAS : pack-years, number of cigarettes, hours per day (0 indicates <1)
6) For overlapping studies: principal rather than subsidiary studies
Finally for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

	Table B11	Table B12
	Low Dose	*High Dose*
N	2	2
NS	2	2
Wt	33.97	20.95
Het Chi	0.86	0.23
Het df	1	1
Het P	N.S.	N.S.
Fixed RR	0.98	1.96
RRl	0.70	1.28
RRu	1.37	3.01
P	N.S.	++
Random RR	0.98	1.96
RRl	0.70	1.28
RRu	1.37	3.01
P	N.S.	++
Asymm P		

Chapter 9

INDUCTION OF ASTHMA – EVIDENCE IN CHILDREN

9.1. THE STUDIES

9.1.1. Studies Identified

Based on the methods described in §7.1, a total of 1106 papers were identified, of which 1103 could be obtained and examined. Of these, 314 contained relevant data and 76 were review papers, with the remaining 713 providing no relevant data at all. The 314 papers related to 227 studies.

Table 9.1 gives certain details of the 227 studies, the six-character reference used to identify the study, a longer study title (which includes information on the location and timing of the study) and the references to the principal publication used to extract the data and to any other relevant publications.

9.1.2. The Study Data

The computer-generated report giving the data recorded on the study database for each of the 227 studies is available from *www.pnlee.co.uk/etsast.htm* [Appendix 13]. Fuller details of studies separating in-life ETS and in utero exposure are given in section 9.3.6.

Table 9.1. The 227 studies considered – children

Study Ref	Study title	Principal publication	Additional publication(s)
ADDOYO	Kumasi paediatric clinic CC (ca 1999?)	Addo-Yobo et al., 2001	-
AGABI1	SIDRIA[1] 10 regions schools CS 1994-95 – children	Agabiti et al., 1999	SIDRIA, 1998; SIDRIA, 1997; Rusconi et al., 1999
AGABI2	SIDRIA 10 regions schools CS 1994-95 – adolescents	Agabiti et al., 1999	SIDRIA, 1998
AGUDOT	Terrassa (Barcelona) schools CS 1997	Agudo Trigueros et al., 2000	-
AKCAKA	Istanbul schools CS 1996-97	Akçakaya et al., 2000	-
ALBA	Barcelona primary care CC 1993	Alba et al., 1996	-
ALDAWO	Al-Khobar City schoolboy CS (ca 1999?)	Al-Dawood, 2000	Al-Dawood, 2001
ALFRA1	Jeddah & Damman population CS 1986-89	Al Frayh et al., 1989	Bener et al., 1991; Al-Frayh et al., 1992
ALFRA2	Riyadh & Damman population CS 1986-89	Al Frayh, 1990	Bener et al., 1991; Al-Frayh et al., 1992
ANDRAE	Rural Sweden (Norrkoping) CS 1985	Andrae et al., 1988	-
ANNES2	French 5-centre schools CS 1993-94	Annesi-maesano et al., 2004	-
ANNESI	Children with parent born 1958 (NCDS[2]) CS 1991	Annesi-maesano et al., 2001	-
ARIF	South Plains/Pan Handle (Texas) household CS 2001	Arif et al., 2004	-
ARSHAD	Isle of Wight allergen avoidance PS 1990-1995	Arshad et al., 1992	Hide et al., 1994; Hide et al., 1996
AZIZI	Kuala Lumpur hospital CC 1989-90	Azizi et al., 1995	-
BALL	Tucson newborns 1980-84 PS to 1997	Ball et al., 2000a	Taussig et al., 1989; Wright et al., 1989; Ball et al., 2000b
BARRET	Ronciglione school CS 1999	Barreto et al., 2001	-
BECKET	Connecticut family hosp CS 1993-1994	Beckett et al., 1996	-
BENCIV	Campania Plain (8 towns) schools CS 2001-02	Bencivenga et al., 2004	-
BENER	Al-Ain urban & rural population CS 1992-93	Bener et al., 1996	-
BERGMA	German Multicentre Allergy Study PS 1990-97	Bergmann et al., 2000	Kulig et al., 1998; Lau et al., 2002
BRABIN	1st Merseyside primary school dust exposure CS 1991	Brabin et al., 1994	-
BURCHF	Tecumseh Community Health 2nd cycle CS 1962-65	Burchfiel et al., 1986	Higgins & Keller, 1975
BURR	South Wales valleys PS 1982 cohort to 1989	Burr et al., 1993	-
BUTZ	Pediatric practices (Baltimore?) CC 1989	Butz & Rosenstein, 1992	-
CALL	Atlanta hospital CC 1990	Call et al., 1992	Moyer, 1993; Platts-Mills & Call, 1993

CELEDO	Costa Rica CC within schools CS 1998-99	Celedón et al., 2001	-
CHEN1	Chang-Ning Shanghai population CS 1985	Chen et al., 1988	-
CHEN2	Humboldt town CS 1993	Chen et al., 1996	-
CHHABR	Delhi schools CS (ca 1997?)	Chhabra et al., 1998	-
CHINN	UK National Study on Health and Growth LS, 1987-88	Chinn & Rona, 1991	Chinn & Rona, 2001
CLARK	Southampton hospital CC (ca 1993?)	Clark et al., 1994	-
CSONKA	Tampere primary schools CS (ca 1999?)	Csonka et al., 2000	-
CUNNI1	24 communities air pollution schools CS 1988-90	Cunningham et al., 1996	Speizer, 1989
CUNNI2	Philadelphia schools air pollution CS 1993	Cunningham et al., 1995	-
DAIGLE	Springville NY pediatric practice CC 1986-87	Daigler et al., 1991	-
DEBENE	Abruzzo schools CS (ca 1993?)	De Benedetto et al., 1994	-
DEKKER	Canadian Air Quality & Health study CC 1988	Dekker et al., 1991	-
DEKOK	Two Dutch region primary schools CS 1993	De Kok et al., 1996	-
DELL	National Longitudinal CS cycle 1 1995-95	Dell & To, 2001	-
DIJKST	Rural SE Netherlands schools PS 2nd phase 1986-87	Dijkstra et al., 1990	Dijkstra et al., 1988
DODGE	Arizona smelter towns school LS 1978-80	Dodge, 1982	Dodge, 1983
DOLD	Munich & South Bavaria primary schools CS 1989-90	Dold et al., 1992	Nicolai et al., 1998
DOTTER	Nikel schools CS 1994	Dotterud et al., 2001	-
DUHME1	Munster schools CS 1994-95 age 5-8	Duhme et al., 1998	-
DUHME2	Munster schools CS 1994-95 age 12-15	Duhme et al., 1998	-
DUHME3	Greifswald schools CS 1995 age 5-8	Duhme et al., 1998	-
DUHME4	Greifswald schools CS 1995 age 12-15	Duhme et al., 1998	-
ECE	Diyarbakir schools CS 1999-2000	Ece et al., 2001	-
EHRLI1	Cape Town elementary schools CC 1993	Ehrlich et al., 1996	Ehrlich et al., 1995a; Ehrlich et al., 1995b
EHRLI2	New York City hospital CC 1988-89	Ehrlich et al., 1992	Lilienfeld et al., 1990; Wartenberg et al., 1994
FAGBUL	Nigerian hospital CC (ca 1992?)	Fagbule & Ekanem, 1994	-
FARBE1	Bogalusa Heart Study CS 1984-85	Farber et al., 1997	-
FARBE2	Bogalusa Heart Study CS 1987-88	Farber et al., 1997	-
FARBE3	Bogalusa Heart Study CS 1992-94	Farber et al., 1997	-

Table 9.1. Continued

Study Ref	Study title	Principal publication	Additional publication(s)
FAROOQ	Oxfordshire GP 1975-84 birth cohort retrospective 1996	Farooqi & Hopkin, 1998	-
FERGUS	Christchurch Child Development 1977 cohort to 1983	Fergusson & Horwood, 1985	Horwood et al., 1985
FIELDE	W Glamorgan primary schools CS 1995	Fielder et al., 1999	-
FLYNN1	Suva City schools CS 1990	Flynn, 1994b	-
FLYNN2	Nausori rural schools CS 1991	Flynn, 1994a	Flynn, 1994b
FORAST	Latium air pollution schools CS 1987	Forastiére et al., 1992	Forastiére, 1992; Wong & Spiegelhalter, 1992
FORSB1	Oslo PEACE[3] CS 1993	Forsberg et al., 1997	-
FORSB2	Kuopio PEACE CS 1993	Forsberg et al., 1997	-
FORSB3	Sweden PEACE CS 1993	Forsberg et al., 1997	-
FREEM1	Passaic Asthma Reduction Effort school-age 1998-2001	Freeman et al., 2003	Freeman et al., 2002
FREEM2	Passaic Asthma Reduction Effort preschool 1998	Freeman et al., 2003	-
FUJI	4 communities air pollution schools CS 1994	Fuji et al., 2002	-
GILLIL	California Children's Health Study baseline 1993, 1996	Gilliland et al., 2001	Peters et al., 1999; Li et al., 2000; London et al., 2001; Gilliland et al., 2002; Gilliland et al., 2003b
GOLD	6 US Cities Longitudinal 1974-	Gold et al., 1993	Ferris, Jr. et al., 1979; Ware et al., 1984; Neas et al., 1994; Wang et al., 1994; Gold et al., 2003
GOREN1	Sharonim power plant schools (grades 2&5) CS 1980	Goren & Goldsmith, 1986	Goren et al., 1991
GOREN2	Coastal towns schools CS 1982-84	Goren & Hellmann, 1995	Goren & Hellman, 1991; Goren et al., 1993
GOREN3	Sharonim power plant schools (grade 8) CS 1980	Goren & Hellmann, 1997	Goren et al., 1991
GOREN4	Sharonim power plant schools (grade 8) CS 1983	Goren & Hellmann, 1997	Goren et al., 1991
GOREN5	Sharonim power plant schools (grade 8) CS 1986	Goren & Hellmann, 1997	Goren et al., 1991
GOREN6	Sharonim power plant schools (grade 8) CS 1989	Goren & Hellmann, 1997	Goren et al., 1991
GORTM1	Genesee County household CS 1977	Gortmaker et al., 1982	-
GORTM2	Berkshire County household CS 1980	Gortmaker et al., 1982	-

GUPTA	Chandigarh schools CS 1997-99	Gupta et al., 2001	-
GURKAN	Dicle hospital CC 1995-97	Gürkan et al., 2002	-
HABY	New South Wales 2 cities pre-school CS 1995	Haby et al., 2001	-
HAJNAL	Swiss nationwide SCARPOL[4] schools CS 1992-93	Hajnal et al., 1999	Braun-Fahrländer et al., 1997
HALONE	Tucson Children's Respiratory 1980-84 birth cohort	Halonen et al., 1999	Martinez et al., 1995; Wright et al., 1996
HJERN1	Swedish Survey Living Conditions CS 1996-97, mothers	Hjern et al., 2001	-
HJERN2	Swedish Survey Living Conditions CS 1996-97, fathers	Hjern et al., 2001	-
HOST	Nordborg schools CS 1990	Høst et al., 1993	-
HU1	Chicago AA[5] Youth Health Behavior Project CS 1994	Hu et al., 1997b	-
HU2	LA and San Diego schools smoking LS 1986-1993	Hu et al., 1997a	-
JAAKK2	Finland all 1987 births PS 1987-94	Jaakkola & Gissler, 2004	-
JAAKKO	Oslo birth cohort 1992-93 PS to 1996	Jaakkola et al., 2001	Nafstad et al., 1997
JANG	Korean schools CS (ca 2002?)	Jang et al., 2004	-
JENKIN	Tasmania schools 1961 cohort CS 1968	Jenkins et al., 1993	-
JONES	Plymouth GP CC 1996	Jones et al., 1999	-
KABESC	Munich and Dresden genotyping CS 1995-96	Kabesch et al., 2004	Weiland et al., 1999
KALYO1	Ankara single school CS 1992	Kalyoncu et al., 1994	-
KALYO2	Ankara single school CS 1997	Kalyoncu et al., 1999	-
KAPLAN	National Child Development Study[2] PS 1958-1964	Kaplan & Mascie-Taylor, 1985	Fogelman, 1980; Anderson et al., 1986; Anderson et al., 1987; Strachan et al., 1988; Anderson et al., 1992; Strachan, 1995; Lewis et al., 1996; Strachan et al., 1996
KARUNA	Gampaha hospital CC 1996-1997	Karunasekera et al., 2001	-
KASPER	Katowice schools LS (stage I) 1996-98	Kasperczyk & Stęplewski, 2002	-
KAY	Birmingham GP CS (ca 1994?)	Kay et al., 1995	-
KEARNE	Cork CS of travelling and settled families 1997	Kearney & Kearney, 1998	-
KELLY	2nd Merseyside primary school dust exposure CS 1993	Kelly et al., 1995	Brabin et al., 1994
KENDIR	Adana schools CS 1993-94	Kendirli et al., 1998	-
KERSHA	Gosport Naval hospital CC 1983-85	Kershaw, 1987	-

Table 9.1. Continued

Study Ref	Study title	Principal publication	Additional publication(s)
KIVITY	Zichron Yaakov & Paradis schools CS (ca 1998?)	Kivity et al., 2001	-
KNIGHT	Toronto pediatrician CS 1993	Knight et al., 1998	-
KUEHR	SW Germany schools baseline CS 1990	Kuehr et al., 1992b	Frischer et al., 1992; Kuehr et al., 1992a; Frischer et al., 1993; Meinert et al., 1994; Henschen et al., 1997
KUHR	Freiburg & Black Forest air pollution family CS 1987-88	Kühr et al., 1991	Mattes et al., 1999
LAM1	Nationwide secondary schools CS 1994	Lam et al., 1998	-
LAM2	Nationwide primary schools CS 1995-96	Lam et al., 1999	-
LAU	HK Island & New Terr schools & kindergartens CS 1989	Lau et al., 1995	-
LEE1	National Korean elementary schools CS 1995	Lee et al., 2001	-
LEE2	National Korean middle schools CS 1995	Lee et al., 2001	-
LEE3	Taiwan nationwide air pollution CS 2001	Lee et al., 2003	-
LEEDER	Harrow 1963-65 birth cohort PS 1963-70	Leeder et al., 1976b	Leeder et al., 1976a
LEEN	Galway primary school CC 1991-92	Leen et al., 1994	Memon & Loftus, 1993
LEROUX	Le Havre primary schools CS 1990-91	Le Roux et al., 1995	-
LEVES1	Quebec schools CS (HSSCY[6]) age 9 1999	Lévesque et al., 2004	-
LEVES2	Quebec schools CS (HSSCY) age 13 1999	Lévesque et al., 2004	-
LEVES3	Quebec schools CS (HSSCY) age 16 1999	Lévesque et al., 2004	-
LILLJE	Oslo birth cohort 1981-84 CS 1991	Lilljeqvist et al., 1997	-
LINDFO	Stockholm hospital CC 1990-92	Lindfors et al., 1995	Lindfors et al., 1994
LIS	Krakow schools CS 1992-95	Lis & Pietrzyk, 1997	-
LISTER	ABS[7] National Health Survey 1989-90	Lister & Jorm, 1998	-
LOPEZC	Lagunera hospital CC (ca 2000?)	López Campos et al., 2001	-
MAIER	Seattle primary schools CS 1994	Maier et al., 1997	-
MARTIN	Tucson COLD[8] PS 1972-1988	Martinez et al., 1992	Lebowitz & Burrows, 1976; Lebowitz et al., 1992
MAVALE	Maputo hospital CC 1999-2000	Mavale-Manuel et al., 2004	-
MCCON1	California Children's Health Study school PS 1993-98	McConnell et al., 2002	Peters et al., 1999; Gilliland et al., 2003a

MCCON2	Rochester NY pediatric practice CS 1980-81	McConnochie & Roghmann, 1986	-
MCKEEV	West Midlands GPRD[9] incidence study (ca 1989-2000?)	McKeever et al., 2001	-
MELIA	UK National Study of Health & Growth LS - 1977	Melia et al., 1981	Somerville et al., 1988
MELSOM	Katmandu Valley schools CC 1997	Melsom et al., 2001	-
MILLER	Manhattan birth cohort PAH[10] to age 2 (ca 2000?)	Miller et al., 2004	Perera et al., 2002
MOHAME	Nairobi primary schools CC 1990-91	Mohamed et al., 1995	-
MONTEF	Nationwide schools CS (ca 1995?)	Montefort et al., 2002	-
MONTEI	Trinidad & Tobago schools CS 2002	Monteil et al., 2004	-
MOUSSA	Al Ain city schools CC 1992-93	Moussa et al., 1996	-
MOYES1	Bay of Plenty primary schools CS (ca 1993?)	Moyes et al., 1995	-
MOYES2	Bay of Plenty secondary schools CS (ca 1993?)	Moyes et al., 1995	-
MUMCUO	Gaza Strip CC 1986-87	Mumcuoglu et al., 1994	-
MURRAY	Vancouver allergy clinic CC 1986-88	Murray & Morrison, 1990	Murray & Morrison, 1989; Murray & Morrison, 1992; Murray & Morrison, 1993
NHANE3	NHANES III[11] nationwide CS 1988-94	Mannino et al., 2001	Gergen et al., 1998; Mannino, 1998; Lanphear et al., 2001; Mannino et al., 2002; Rodriguez et al., 2002
NICOLA	Munich schools traffic CS 1995-96	Nicolai et al., 2003	-
NILSSO	Ostergotland population CS (ca 1998?)	Nilsson et al., 1999	-
NITTA	Tokyo and Ibaraki schools pollution CS 1995	Nitta et al., 1996	-
NYSTAD	Oslo schools CS 1994-95	Nystad et al., 1999	-
OCONNE	Minnesota clinic CC 1969-1971	O'Connell & Logan, 1974	-
ODDY	Western Australia pregnancy cohort 1989-92 to 1998	Oddy et al., 1999	-
OHARA	Sendai & Fukushima schools & nurseries CS 2001	Ohara et al., 2002	-
OLIVET	Cleveland AA[5] hospital CC 1993-94	Oliveti et al., 1996	-
PALMIE	Italy (Naples?) CC (ca 1988?)	Palmieri et al., 1990	-
PETERS	2 districts air pollution schools PS 1989-91	Peters et al., 1996	-
PIC	Auvergne schools CS 1999-2000	Pic et al., 2002	-
PIROGO	Family Practice CS (ca 2003? Wroclaw?)	Pirogowicz et al., 2004	-

Table 9.1. Continued

Study Ref	Study title	Principal publication	Additional publication(s)
POKHAR	Haryana village schools CC 1995-96	Pokharel et al., 2001	-
PONSON	Tasmania linked SIDS[12] PS and schools CS 1988-95	Ponsonby et al., 2000	-
QIAN	Three Chinese city school CS 1988-89	Qian et al., 2000	-
RASANE	Finnish twins birth cohort 1975-79 CS 1995	Räsänen et al., 2000	-
RATAGE	Delhi hospital CC 1996-98	Ratageri et al., 2000	-
RENNIE	Saskatchewan farming/Hutterite CS 1993	Rennie et al., 2002	-
RIBEIR	Sao Paulo kindergarten/elementary school 1996	Ribeiro et al., 2002	-
RONCH1	Rome primary schools CS 1974	Ronchetti et al., 2001	Ronchetti et al., 1982; Bonci et al., 1993
RONCH2	Rome primary schools CS 1992	Ronchetti et al., 2001	Bonci et al., 1993; Ronchetti et al., 2002
RONCH3	Rome primary schools CS 1998	Ronchetti et al., 2001	Ronchetti et al., 2002
RONMA1	Norbotten primary school baseline 1996	Rönmark et al., 1998	Rönmark et al., 1999; Rönmark et al., 2001; Rönmark et al., 2002; Perzanowski et al., 2002
RONMA2	Norbotten primary school CS 1997	Rönmark et al., 2001	Rönmark et al., 1998; Rönmark et al., 1999; Rönmark et al., 2002; Perzanowski et al., 2002
RONMA3	Norbotten primary school PS 1996-99	Rönmark et al., 2002	Rönmark et al., 1998; Rönmark et al., 1999; Rönmark et al., 2001; Perzanowski et al., 2002
ROSASV	Mexico allergy clinic CC (ca 2001?)	Rosas Vargas et al., 2002	-
RUDNIK	Cracow & Limanowa air pollution LS 1974-1980	Rudnik et al., 1985	-
SANZOR	Valencia schools CS (ca 1988?)	Sanz Ortega et al., 1990	-
SARRAZ	Mexico allergy clinic CC (ca 1996?)	Sarrazola Sanjuan et al., 1997	-
SCHENK	Chestnut Ridge school CS 1979	Schenker et al., 1983	-
SCHMIT	Austrian Tyrol air pollution schools CS 1989	Schmitzberger et al., 1993	-
SELCUK	Edirne schools CS 1994	Selçuk et al., 1997	-
SENNHA	Swiss household CS 1990	Sennhauser & Güntert, 1992	-
SHAMS2	NE England schools CS age 13-14 (ca 1998?)	Shamssain & Shamsian, 2001	-

SHAMSS	NE England schools CS (ca 1998?)	Shamssain & Shamsian, 1999	-
SHERMA	East Boston school LS 1975-88	Sherman et al., 1990	Tager et al., 1979; Weiss et al., 1980; O'Connor et al., 1987; Carey et al., 1996
SHIVA	Tehran hospital CS 2001	Shiva et al., 2003	-
SHOHAT	National schools CS 1997	Shohat et al., 2002	-
SIGURS	Boras hospital bronchiolitis PS 1989-93	Sigurs et al., 1995	-
SOMERV	UK National Study of Health & Growth LS - 1982	Somerville et al., 1988	Chinn & Rona, 2001
SOTOQU	Costa Rica schools CS 1987	Soto-Quiros et al., 1994	-
SOYSET	Western Norway schools CS 1989-92	Søyseth et al., 1995	-
SPENGL	Sverdlovsk 9 city housing CS (ca 2002?)	Spengler et al., 2004	-
SPIEKE	SW Germany schools cotinine PS 1990-92	Spiekerkötter et al., 1994	Henschen et al., 1997; Kuehr et al., 1998
SQUILL	Central Virginia schools CC 1992-93	Squillace et al., 1997	-
STANHO	Wairoa school CS 1975	Stanhope et al., 1979	-
STAZI	Basilicata infant vaccination CS 1993-94	Stazi et al., 2002	Annesi-maesano et al., 1996
STERN1	Ontario & Manitoba air pollution schools CS 1983	Stern et al., 1989a	-
STERN2	Ontario & Saskatchewan schools CS (ca 1986?)	Stern et al., 1989b	Stern et al., 1987
STODDA	US National Medical Expenditure household CS 1987	Stoddard & Miller, 1995	-
STRACH	Sheffield schools CC 1993	Strachan & Carey, 1995	-
STURM	North Carolina schools CS 1999-2000	Sturm et al., 2004	-
TARIQ	Isle of Wight birth cohort 1989-90 PS to 2000	Tariq et al., 2000	Arshad & Hide, 1992; Arshad et al., 1993; Tariq et al., 1995; Tariq et al., 1998; Kurukulaaratchy et al., 2002; Kurukulaaratchy et al., 2004
TAYLOR	British Births Survey PS 1970 cohort to 1986	Taylor et al., 1983	Neuspiel et al., 1989; Lewis et al., 1996
TIMONE	Kuopio schools pollution CS 1993	Timonen et al., 1995	-
TOMINA	Aichi clinic CS 1978-79	Tominaga & Itoh, 1985	-
TSIMOY	Nassau county athletes CS 1985	Tsimoyianis et al., 1987	-
ULRIK	Copenhagen district PS 1986-1992	Ulrik et al., 1996	Ulrik et al., 1998
VARELA	Mexico City schools SPT[13] CS 1999-2000	Varela Delgado et al., 2001	-

Table 9.1. Continued

Study Ref	Study title	Principal publication	Additional publication(s)
VAVILI	Genotyping CC (Novosibirsk ca 1999?)	Vavilin et al., 2000	Vavilin et al., 2002
VENNER	Anqing CS of asthma index families 1995-98	Venners et al., 2001	Xu et al., 1999b
VERHOE	School respiratory CC (Amsterdam ca 1990?)	Verhoeff et al., 1992	-
VOLKME	South Australia preschool CS 1993	Volkmer et al., 1995a	Volkmer et al., 1995b
VONMAF	Virginia & Connecticut family hospital CS 1993-1996	Von Maffei et al., 2001	-
WANG	2 areas schools air pollution CS 1995-96	Wang et al., 1999	-
WARKE	Belfast hospital CC (ca 2002?)	Warke et al., 2003	-
WEITZ1	National Health Interview Survey Suppl 1981 Age 0-5	Weitzman et al., 1990b	Weitzman et al., 1990a
WEITZ2	National Health Interview Survey Suppl 1981 Age 6-17	Weitzman et al., 1990a	Weitzman et al., 1990b
WICKMA	Stockholm BAMSE[14] birth cohort 1994-96 for 2 years	Wickman et al., 2003	Lannerö et al., 2002
WIJGA	Netherlands PIAMA[15] PS to age 3 1996-2000	Wijga et al., 2003	Brunekreef et al., 2002
WILLE1	Malmo hospital/school CC study 1987-88	Willers et al., 1991	-
WILLE2	Malmo population cotinine CC 1993	Willers et al., 2000	Forsberg et al., 1997
WITHER	Southampton GP birth cohort 78-80 follow-up CS 1995	Withers et al., 1998	-
WOLFO1	SW Germany urban/rural phase 1 CS 1977	Wolf-Ostermann et al., 1995	Luttmann et al., 1993
WOLFO2	SW Germany urban/rural phase 2 CS 1979	Wolf-Ostermann et al., 1995	Luttmann et al., 1993
WOLFO3	SW Germany urban/rural phase 3 CS 1985	Wolf-Ostermann et al., 1995	Luttmann et al., 1993
XU	Northern Finland birth cohort 1985-86 PS to 1993	Xu et al., 1999a	-
YANG	Rural Kaohsiung schools CS 1994	Yang et al., 1997	Yang et al., 1998
YUAN	North Jutland whole birth cohort 1996-97 to 1 year	Yuan et al., 2003	-
ZEIGER	San Diego high risk birth cohort 1981-84 to 1991	Zeiger & Heller, 1995	Zeiger et al., 1989
ZEJDA	Upper Silesia primary school air pollution CS (ca 1994?)	Zejda et al., 1996	-
ZHANG	Four Chinese Cities Study school/family CS 1993-96	Zhang et al., 2002	Qian et al., 2004
ZHENG	Shunyi Beijing schools CC 1999-2001	Zheng et al., 2002	-

CC = case-control study; CS = cross-sectional study; PS = prospective study; LS = longitudinal study; GP = general practitioner.
(SE = south east in this Table only.)

[1] SIDRIA = Studi Italiani sui Disturbi Respiratori nell'Infanzia e l'Ambiente (Italian Studies on Respiratory Disorders in Childhood and the Environment).

[2] NCDS = National Child Development Study.

[3] PEACE = Pollution Effects on Asthmatic Children in Europe.
[4] SCARPOL=Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen.
[5] AA = African-American.
[6] HSSCY = Health and Social Survey of Quebec Children and Youth.
[7] ABS = Australian Bureau of Statistics.
[8] COLD = chronic obstructive lung disease.
[9] GPRD = General Practice Research Database.
[10] PAH = polycyclic aromatic hydrocarbons.
[11] NHANES III = Third National Health and Nutrition Examination Survey
[12] SIDS = sudden infant death syndrome.
[13] SPT = skin prick test.
[14] BAMSE B = children, A=allergy, M=environment, S=Stockholm, E=epidemiology.
[15] PIAMA = Prevention and Incidence of Asthma and Mite Allergy.

9.1.3. Overlapping Studies

As discussed in §7.6, there are potential problems with overlapping studies. There were six sets of studies with a modest degree of overlap, which cannot be disentangled and which it was decided to ignore. These sets are described below briefly:

1. Results from the annual UK National Study on Health and Growth were available for 1977 (MELIA), 1982 (SOMERV) and 1987-88 (CHINN). The study included ages 5-11, so that the youngest children in each reported phase of the study would also have been included in the following phase. However this overlap was small – stated to be 5% between 1982 and 1988. During the 1980s, additional study areas were added for England and these were studied in alternate years to the original areas, so that there is no overlap for the English areas between 1987 and 1988. For the Scottish areas the position is unclear and it seems likely that at least some areas were repeated between 1987 and 1988. However as the results are only available for 1987 and 1988 combined, there was no satisfactory alternative to including both years. There is also a possibility of some overlap with the British Births Survey (TAYLOR), which included all children born in a single week in 1970, who would thus have been in the eligible age range for MELIA in 1977.
2. JAAKK2 is a prospective study of all singleton children born in 1987 in Finland, up to age 7. Some of those children may also have participated in study CSONKA, a cross-sectional study of 6-13 year olds in Tampere. This study was published in 2000 although the date when it was carried out was not stated.
3. In the Swedish Survey of Living Conditions, a random sample of adults was drawn and the results presented here refer to their children. These have been entered on the database as separate studies according to whether the adult respondent was the mother (HJERN1) or father (HJERN2), because they are effectively independent subsets. However an apparent discrepancy in the numbers suggests that 10 children (0.2%) may have been in both parts.
4. Two Canadian studies of 7-12 year olds may have overlapped. Tillonsburg is one of two towns included in STERN1 in 1983, and one of 10 towns in STERN2. The timing of STERN2 is not stated, but it was probably only a few years later, so that the youngest children from STERN1 would have been included again.
5. Three identically designed cross-sectional studies were carried out in SW Germany, including the same cohort of children on each occasion, when they were in 2nd grade in 1977 (WOLFO1), 4th grade in 1979 (WOLFO2) and 10th grade in 1985 (WOLFO3). However, relatively few children were included more than once (17% included in all three phases, and a further 24% included twice).
6. Two studies were carried out in 1995-96, KABESC including 9-11 year olds from Munich (37% of subjects) and Dresden, while NICOLA included 5-7 and 9-11 year olds in Munich only. Thus the Munich 9-11 year olds may have been included in both studies.

There were also seven sets of studies which clearly do overlap, where one member of the set, marked as the “principal study,” contains the most appropriate data. For others, marked as

"subsidiary studies," RRs are only included in meta-analyses if equivalent results are not available from the principal study. These sets are described below:

1. A series of studies were carried out in three towns in Northern Sweden, with all children in grades 1 and 2 (age 7-8) invited to participate in 1996, all in grades 2 and 3 in 1997 and so on to 1999. Participation in subsequent years was not restricted to those who participated in 1996. Results from the baseline prevalence study (RONMA1) and results of follow-up of those children who participated and were asthma-free at baseline (RONMA3) are independent and have both been entered as principal studies. A cross-sectional analysis of the 1997 survey has been entered as subsidiary (RONMA2).
2. KUEHR is a baseline prevalence study, and has been designated as a principal study. SPIEKE is a follow-up study of less than half the original subjects, not restricted to those who were asthma-free at baseline, and has been designated as the subsidiary study.
3. The Bogalusa Heart Study gave results from three surveys within a 10 year period, including all children aged 5-17 (or 7-17). This clearly involved substantial overlap. The middle phase (FARBE2 – 1987-8) was designated as the principal study and the first (FARBE1 – 1984-5) and last (FARBE3 – 1992-4) as subsidiaries.
4. Results are available from two studies of 5-11 year olds conducted in two schools two years apart. The first (BRABIN – 1991) used a 50% random sample while the second (KELLY – 1993) included all children. A substantial proportion of children participated in both surveys (58% of BRABIN subjects also participated in KELLY). Although it had the smaller sample, BRABIN (1991) has been designated as the principal study because it gave actual RR results, whereas KELLY (1993) merely stated that the results were non-significant.
5. FORSB3 is a cross-sectional study conducted in two areas. All the asthmatic children from one area only (Malmo) were also included in a second study WILLE2, together with a small number of the symptom-free children as controls. This second study was marked as subsidiary.
6. Similar studies were conducted in three regions of Saudi Arabia – Jeddah, Damman and Riyadh. Although results for all three areas combined were available (Bener et al., 1991), these were not entered because of apparent inconsistencies. (The only results were from a multiple logistic regression and the SEs given were completely inconsistent with the total number of subjects in the study). Less unsatisfactory[10] unadjusted results were available and were entered, as study ALFRA1 (principal) for Jeddah and Damman, and as ALFRA2 (subsidiary) for Damman and Riyadh. Adjusted results for ALFRA1 which appeared to suffer from the same problem as the combined results were entered without their suspect CIs, and one rather vague result relevant to all three regions was also entered under study ALFRA1.
7. A series of cross-sectional school studies were carried out at three year intervals in the vicinity of a power plant in Israel. Results from the first study (1980) were for children in school grades 2, 5, and 8, and for convenience, this was split and entered as GOREN1 for grades 2 and 5, and as GOREN3 for grade 8. Results from the later

[10] See also Table 9.7

studies were for grade 8 only. Thus the children in the 1983 study (GOREN4) were largely those who had been included as grade 5 in 1980, and similarly those in the 1986 study (GOREN5) had been included as grade 2 in 1980, and so these were designated as subsidiary studies. The final study in 1989 (GOREN6) did not overlap. (Note that GOREN2 is an unrelated study.)

9.1.4. Study Characteristics

Table 9.2 gives the distribution of various selected study characteristics by study type and overall. Except where specified otherwise, the discussion in the rest of this section refers to the principal studies only.

Table 9.2. Characteristics of the 227 studies – children

Characteristic : Level		Number of studies by study type[1]				
		CC	Prosp	CrSec	Subsid	Total
Total		42	32	143	10	227
Study type :	case-control	42	0	0	1	43
	prospective	0	32	0	1	33
	cross-sectional	0	0	143	8	151
Study sex :	both	42	32	141	10	225
	male	0	0	2	0	2
Lowest age in study :						
	0	5	23	15	0	43
	1	5	0	5	0	10
	2	1	0	1	0	2
	3	6	0	7	0	13
	4	3	0	4	0	7
	5	4	1	15	3	23
	6	6	1	34	1	42
	7	2	2	18	2	24
	8	2	3	10	2	17
	9	2	1	8	0	11
	10	1	0	4	0	5
	11	2	0	1	0	3
	12	0	0	8	0	8
	13	2	1	8	2	13
	14	0	0	2	0	2
	16	0	0	3	0	3
	missing	1	0	0	0	1
Highest age in study (for prospective studies refers to baseline) :						
	0	0	21	0	0	21
	1	0	1	2	0	3
	3	1	0	1	0	2
	4	2	0	2	0	4
	5	2	1	5	0	8

	7	2	0	5	0	7
	8	2	1	5	2	10
	9	3	1	5	1	10
	10	4	1	5	0	10
	11	2	0	20	1	23
	12	2	1	19	1	23
	13	2	0	6	1	9
	14	3	0	18	2	23
	15	7	1	16	0	24
	16	3	1	11	0	15
	17	2	1	16	2	21
	18	3	0	3	0	6
	19	0	0	2	0	2
	20	0	0	1	0	1
	21	0	0	1	0	1
	missing	2	2	0	0	4
Highest age in study at final follow-up (prospective studies) :						
	1	-	1	-	0	1
	2	-	2	-	0	2
	3	-	2	-	0	2
	4	-	2	-	0	2
	5	-	1	-	0	1
	6	-	2	-	0	2
	7	-	7	-	0	7
	10	-	1	-	1	2
	11	-	3	-	0	3
	12	-	2	-	0	2
	13	-	1	-	0	1
	14	-	1	-	0	1
	16	-	2	-	0	2
	18	-	2	-	0	2
	22	-	1	-	0	1
	23	-	2	-	0	2
Study race :	all (in country)	38	29	134	8	209
	whites (including Hispanics)	2	0	3	0	5
	blacks	2	0	1	0	3
	whites and blacks	0	2	2	2	6
	whites (excluding Hispanics)	0	1	0	0	1
	Chinese	0	0	1	0	1
	Fijians and Indians	0	0	1	0	1
	Han Chinese	0	0	1	0	1
Continent :	N America	9	10	32	2	53
	S/C America	4	0	4	0	8
	W Europe/Scandinavia	14	17	57	5	93
	E Europe/Balkans	2	1	12	0	15
	Asia	8	1	29	3	41
	Australasia	0	3	9	0	12
	Africa	5	0	0	0	5
Country :	USA	7	10	21	2	40
	USA and Canada	0	0	1	0	1

Table 9.2. (continued)

Characteristic : Level		Number of studies by study type[1]				
		CC	Prosp	CrSec	Subsid	Total
US state :	all	0	0	4	0	4
	Cal,Wash,Oreg	0	3	2	0	5
	Nev,Ut,Ariz,Tex	0	4	1	0	5
	Minn,Ia,Wis,Ill,Mo	1	0	1	0	2
	Ark,Miss,La,Al	0	0	1	2	3
	Mich,Ind,Oh,Tenn	1	0	2	0	3
	Fla,Ga,SC,NC	1	0	1	0	2
	Pa,NJ,Md,WVa,Va,Del,WasDC	2	0	4	0	6
	Vt,Me,NY,NH,Mass,RI,Conn	2	2	4	0	8
	multi (but not all)	0	1	2	0	3
Country	Canada	2	0	10	0	12
(cont'd)	Costa Rica	1	0	1	0	2
	Brazil	0	-	1	-	1
	Mexico	3	-	1	-	4
	Trinidad & Tobago	0	-	1	-	1
	UK	6	7	11	1	25
	Ireland	1	0	1	0	2
	Denmark	0	2	1	0	3
	Norway	0	1	4	0	5
	Sweden	2	3	6	2	13
	Finland	0	2	4	0	6
	Spain	1	0	2	0	3
	France	0	0	3	0	3
	Netherlands	1	1	2	0	4
	Switzerland	0	0	2	0	2
	Germany	0	1	11	2	14
	Austria	0	0	1	0	1
	Italy	3	0	8	0	11
	Malta	0	0	1	0	1
	Poland	0	1	4	0	5
	Turkey	1	0	6	0	7
	Russia	1	0	2	0	3
	Japan	0	0	4	0	4
	China	1	0	4	0	5
	Hong Kong	0	1	3	0	4
	Malaysia	1	0	0	0	1
	India	2	0	2	0	4
	Nepal	1	0	0	0	1
	Saudi Arabia	0	0	2	1	3
	UAE	1	0	1	0	2
	Taiwan	0	0	3	0	3
	Israel	1	0	6	2	9
	Sri Lanka	1	0	0	0	1
	Korea	0	0	3	0	3

Iran	0	0	1	0	1
Australia	0	2	4	0	6
New Zealand	0	1	3	0	4
Fiji	0	0	2	0	2
Ghana	1	0	0	0	1
Kenya	1	0	0	0	1
Nigeria	1	0	0	0	1
South Africa	1	0	0	0	1
Mozambique	1	0	0	0	1
Start year of study :					
before 1960	0	1	0	0	1
1960-1969	1	1	2	0	4
1970-1979	0	7	9	0	16
1980-1989	9	13	31	4	57
1990-1999	22	8	77	6	113
2000-2001	0	0	6	0	6
missing	10	2	18	0	30
End year of study (for prospective studies refers to baseline) :					
before 1960	0	1	0	0	1
1960-1969	0	1	2	0	3
1970-1979	1	6	8	0	15
1980-1989	7	11	26	4	48
1990-1999	22	11	78	6	117
2000-2001	2	0	11	0	13
missing	10	2	18	0	30
Final follow-up year (prospective studies) :					
1960-1969	-	1	-	0	1
1970-1979	-	1	-	0	1
1980-1989	-	8	-	0	8
1990-1999	-	19	-	1	20
missing	-	2	-	0	2
Principal publication year :					
1970-1979	1	1	1	0	3
1980-1989	1	5	14	0	20
1990-1999	27	13	74	8	122
2000-2002	13	13	54	2	82
Type of population[2] (for CC studies refers to cases) :					
all children	0	7	7	1	15
random children	0	3	13	1	17
all schoolchildren	4	2	19	3	28
random schoolchildren	7	2	45	3	57
all in given school(s)	2	1	20	0	23
random in given school(s)	0	1	2	0	3
schoolchildren NOS	1	2	12	2	17

Table 9.2. (continued)

Characteristic : Level	Number of studies by study type[1]				
	CC	Prosp	CrSec	Subsid	Total
all hospital/clinic patients	2	0	1	0	3
random hospital/clinic patients	0	1	0	0	1
all patients in given hospital/clinic(s)	10	0	2	0	12
random patients in given hospital/ clinic(s)	3	0	0	0	3
hospital NOS	4	1	0	0	5
all primary care patients	0	0	1	0	1
random primary care patients	1	0	0	0	1
all patients at given primary care(s)	4	1	2	0	7
random patients at given primary care(s)	0	0	1	0	1
primary care NOS	2	0	1	0	3
all children attending pre-school routine health check	0	0	1	0	1
all children receiving primary care at hospital clinic who had been born same hospital	1	0	0	0	1
all children from random households	0	0	6	0	6
all newborns at given hospital(s)	0	4	1	0	5
families of all newborns delivered at given hospital(s)	0	0	2	0	2
random newborns at given hospital(s)	0	1	0	0	1
all children of random parent who had participated in NCDS	0	0	1	0	1
all children hospitalized with bronchiolitis at given hospital + population controls	0	1	0	0	1
all children from all asthmatic families	0	0	1	0	1
all patients at given hospital with high allergy risk	0	2	0	0	2
all patients at given primary care with high allergy risk	0	1	0	0	1
random athletes in given school(s)	0	0	1	0	1
all twins still resident in country of birth	0	0	1	0	1
all schoolchildren living on farms	0	0	1	0	1
random newborns with high SIDS risk	0	1	0	0	1
all travellers' children + all at given school	0	0	1	0	1
unspecified	1	0	0	0	1
Type of controls :					
healthy	29	-	-	1	30
diseased/hospital	13	-	-	0	13

Type of control population :					
same as cases	19	-	-	1	20
same as cases but excluding children with resp symptoms, allergy or history of asthma	15	-	-	0	15
all at given school(s)	1	-	-	0	1
random at given schools excluding children with respiratory symptoms or history of asthma	2	-	-	0	2
random schoolchildren excluding children using asthma medication	1	-	-	0	1
random children from hospital catchment area	1	-	-	0	1
random children from hospital catchment area with no history of asthma	1	-	-	0	1
no siblings with allergic disorders	1	-	-	0	1
all newborns	1	-	-	0	1
Matched on sex	13	-	-	1	14
Matched on age	19	-	-	1	20
Matched on race	2	-	-	0	2
Matched on location	7	-	-	1	8
Matched on SES	2	-	-	0	2
Matched on hospital admission	1	-	-	0	1
Respondent (for ETS exposure information) :					
child	3	0	17	0	20
parent	29	23	103	10	165
medical records	2	3	1	0	6
parent and child	2	6	16	0	24
unspecified (parent/child)	5	0	1	0	6
household member or accompanying adult	1	0	3	0	4
parent or child (depending on age)	0	0	2	0	2
Standard questionnaire[3] :					
no	30	25	74	6	135
ISAAC	8	3	37	2	50
ATS/NHLI/ESP	2	3	20	2	27
MRC	1	0	2	0	3
IUATLD	1	0	2	0	3
WHO	0	1	7	0	8
ICHPPC	0	0	1	0	1
Lifetime[4]/incidence asthma available :					
no	29	8	46	2	85
yes	13	24	97	8	142

Table 9.2. (continued)

Characteristic : Level	Number of studies by study type[1]				
	CC	Prosp	CrSec	Subsid	Total
Source of lifetime[4]/ incidence asthma diagnosis :					
medical records	6	6	2	0	14
parent report (physician diagnosis)	0	6	42	3	51
parent report (other/unspec/mixed)	1	6	33	5	45
child report (physician diagnosis)	0	2	7	0	9
child report (other/unspecified/mixed)	1	1	7	0	9
medical records or parent report (physician diagnosis)	1	1	2	0	4
medical records or parent report (other/ unspecified/mixed)	1	0	0	0	1
parent or child report (physician diagnosis)	0	1	1	0	2
parent or child report (other/unspecified/mixed)	1	1	2	0	4
unspecified	2	0	1	0	3
Timing of lifetime[4] asthma :					
lifetime	5	3	69	7	84
unspecified	8	2	26	0	36
from age 2	0	0	1	0	1
from age 3	0	0	1	0	1
up to baseline	0	0	0	1	1
NA (incidence only)	0	19	0	0	19
Timing of incidence asthma :					
since baseline (earlier excl)	0	4	0	0	4
lifetime (recruit at birth)	0	15	0	0	15
lifetime (retrospective)	0	1	0	0	1
NA (prevalence analysis only)	13	4	96	8	121
Number of lifetime[4]/ incidence asthma cases :					
1-100	4	9	27	3	43
101-200	8	2	25	2	37
201-500	1	8	23	2	34
501-1000	0	2	12	1	15
>1000	0	2	5	0	7
median	107	242	176	161	168.5[5]
min	40	12	6	50	6
max	400	5842	3178	748	5842
missing	0	1	5	0	6
Current asthma available :					
no	13	21	78	8	120
yes	29	11	65	2	107
Current asthma is first occurrence	3	0	0	0	3
Repeat measures for current asthma (prospective studies)	-	7	-	0	7

Source of current asthma diagnosis :					
medical records	19	1	2	1	23
parent report (physician diagnosis)	0	1	10	0	11
parent report (other/ unspecified/mixed)	7	6	34	1	48
child report (physician diagnosis)	0	0	2	0	2
child report (other/ unspecified/mixed)	2	1	15	0	18
medical records or parent report (physician diagnosis)	1	1	0	0	2
parent or child report (physician diagnosis)	0	1	0	0	1
parent or child report (other/unspecified/mixed)	0	0	2	0	2
Timing of current asthma :					
current diagnosis	13	0	2	1	16
last n months (n<6)	0	1	5	0	6
last n months (6<=n<12)	1	0	1	0	2
last n months (12<=n<24)	11	7	42	1	61
last n years (2<=n<5)	0	0	1	0	1
current NOS	4	3	14	0	21
Number of current asthma cases :					
1-100	10	3	28	1	42
101-200	9	5	12	0	26
201-500	7	2	11	1	21
501-1000	2	0	7	0	9
>1000	1	0	2	0	3
median	137	164.5	116	189.5	137[6]
min	14	26	8	85	8
max	1306	470	20637	294	20637
missing	0	1	5	0	6
Total number of subjects :					
1-100	5	0	1	0	6
101-200	8	2	6	1	17
201-500	17	4	8	0	29
501-1000	7	5	19	3	34
>1000	5	21	108	6	140
median	250	1677	2205.5	1974	1596.5[7]
min	35	140	57	111	35
max	16445	56632	155284	3746	155284
missing	0	0	1	0	1
Other definitions of asthma available	7	5	32	1	45
Wheezing/wheezing bronchitis available	5	20	71	5	101
Other exposures available	3	4	8	1	16

Table 9.2. (continued)

Characteristic : Level	Number of studies by study type[1]				
	CC	Prosp	CrSec	Subsid	Total
Child smokes : no mention	34	23	105	10	172
smokers excluded biochemically	0	0	1	0	1
smokers excluded questionnaire	0	0	11	0	11
smokers excluded unspecified	0	0	1	0	1
smokers above given age excluded (below assumed to be non-smokers)	0	0	2	0	2
no smokers found above given age (below assumed to be non-smokers)	1	1	0	0	2
assumed no smokers	1	1	1	0	3
no smokers NOS	0	0	1	0	1
smokers included but stated to be few	0	2	2	0	4
smokers included	2	2	7	0	11
smokers included and adjusted for in analysis	1	1	3	0	5
smokers included because active smoking was tested in univariate analysis and found not significant	0	0	1	0	1
smokers included because active smoking rejected from multiple logistic regression due to lack of significance	0	1	1	0	2
discussed, but no data available	1	0	5	0	6
biochemical exclusion discussed but not used	1	0	0	0	1
no mention in analysis but was in questionnaire	1	1	0	0	2
Other results for child smokers available	2	5	13	0	20
Total number of adjustment factors used :					
none	20	7	55	4	86
1	4	2	1	0	7
2	2	2	7	1	12
3	1	1	12	2	16
4-5	6	5	16	2	29
6-10	6	12	39	1	58
11+	3	3	13	0	19
Confounders considered[8]					
- sex	9	20	64	4	97
- age	9	4	45	3	61
- race	3	5	15	2	25
- location within study area (including urban/rural, air pollution)	7	6	37	2	52
- type of respondent	3	0	5	0	8
- interview setting	0	1	2	0	3
- year of diagnosis	0	1	0	0	1
- family medical history (parent/sibling) :					

(by 1-3 variables)	9	14	46	3	72
(by 4-6 variables)	1	2	0	0	3
- parent's age	0	4	6	0	10
- SES or parental education (by 1-4 variables)	9	16	40	2	67
- household composition (number of children, single parent, position in sibship etc)	2	9	24	0	35
- day care	0	2	5	0	7
- air conditioning, humidifier (by 1-4 variables)	2	1	6	0	9
- cooking & heating methods, incense, mosquito coils :					
(by 1-3 variables)	7	1	26	2	36
(by 4-5 variables)	1	0	3	0	4
- damp or mould in home	6	2	18	1	27
- housing quality, age, size, crowding, shared bedroom, owned/rented :					
(by 1-3 variables)	7	2	16	2	27
(by 4-6 variables)	0	0	1	0	1
- pets or close animal contact	4	5	23	1	33
- exposure to food or housedust allergens, carpets, type of bedding, houseplants	3	1	9	0	13
- farming	0	0	2	0	2
- religion	0	0	1	0	1
- mobility (e.g. parent or child born abroad, moved house, time of residence, language spoken at home)	0	0	6	0	6
- child's medical history/symptoms (including breastfeeding and SPT results) :					
(by 1-3 variables)	10	14	29	1	54
(by 4-11 variables)	1	3	4	0	8
- obesity/body mass index	0	1	9	0	10
- exercise	0	0	1	0	1
- diet (excluding breastfeeding)	0	1	1	0	2
- child active smoking	1	1	3	0	5
- maternal smoking in pregnancy	3	1	10	0	14
- parental smoking current/since birth	6	3	21	0	30
- household ETS exposure	4	1	3	0	8
Other confounders considered but rejected	8	6	25	0	39
Results by other stratifying factors available	12	11	26	1	50

[1] CC = case-control; Prosp = prospective; CrSec = Cross-sectional; Subsid = Subsidiary; see also §9.1.4 "Design"

[2] Refers to children within the study area, age group etc as defined by other variables. "Random schoolchildren" includes "all children from randomly selected schools" and "randomly selected children from all schools," and similarly for hospital and primary care.

[3] ISAAC = International study of asthma and allergies in childhood, ATS = American Thoracic Society, NHLI = National Heart and Lung Institute, ESP = Epidemiology standardization project, MRC = Medical Research Council, IUATLD = International Union Against Tuberculosis and Lung Disease, WHO = World Health Organization, ICHPPC = International classification of health problems in primary care.

[4] Includes asthma of unspecified timing.

[5] Median, min and max are the same when based on the 128 principal studies only with data.

[6] Median, min and max are the same when based on the 99 principal studies only with data.

[7] Median is 1568.5 when based on the 216 principal studies only with data, min and max are the same.

[8] By up to 3 variables, unless stated otherwise.

Design. Of the 217 principal studies, 42 were case-control, 32 prospective, and 143 of cross-sectional design. The 10 subsidiary studies comprised one case-control, one prospective and eight of cross-sectional design. The case-control studies included nine principal and one subsidiary studies where an initial cross-sectional phase was carried out to identify cases (CELEDO, EHRLI1, LEEN, MELSOM, MOHAME, POKHAR, SQUILL, STRACH, WILLE2, ZHENG), and three studies conducted as cross-sectional but analysed as case-control (AGABI1, AGABI2, DEKKER). Note that cross-sectional is taken to include studies where only the baseline phase of a prospective study, or only one phase of a longitudinal study, provided relevant results; it also includes each phase of a longitudinal study where children from specific schools were repeatedly recruited but no effort was made to link results for individual children between phases. "Prospective" was taken to include three studies designed as intervention trials (on allergen avoidance – ARSHAD, ZEIGER and on ultrasonography – ODDY) and one designed as a case-control study of bronchiolitis (SIGURS) which were analysed ignoring their original status, and one study (MCKEEV) which retrospectively collected primary care records from birth including date of diagnosis of asthma.

Sexes considered. All studies included both sexes, except two which considered males only (KEARNE in Ireland and ALDAWO in Saudi Arabia).

Age of subjects[11]. The lower age limit was below 5 for 75 studies, in the range 5-9 for 109, and 10 or more for 32. For the case-control and cross-sectional studies, the upper age limit was below 10 for 37 studies, in the range 10-14 for 81, 15-18 for 61 and 19-21 for four. For the prospective studies, the age at final follow-up was under 10 for 17 studies, 10-18 for 12 and 22-23 for three.

Race of subjects. In 201 studies, there was no selection on race though clearly variation in the location of the study would cause major variation in the racial distribution. In six studies (2 in USA, 1 in UK, 1 in Germany, 1 in Italy and 1 in Russia), subjects were specifically restricted to whites. In five other studies, subjects were specifically restricted to a race other than white (blacks in 3 US studies, Han Chinese in 1 Chinese study, Chinese in 1 Hong Kong study), and in five further studies to two races (whites and blacks in 4 US studies, and Fijians and Indians in a Fijian study).

Location. Studies were most commonly conducted in West Europe or Scandinavia (41%), North America (24%), and Asia or Middle East (18%), and less commonly conducted in East Europe or the Balkans (7%), Australasia (6%), South or Central America (4%), and Africa (2%). Apart from the fact that all five African studies were of case-control design, while none in Australasia were, the distribution of study types was similar within each region.

Of the 88 studies conducted in West Europe or Scandinavia, 24 were conducted in the UK, 12 in Germany, 11 in Italy and 11 in Sweden with studies also conducted less commonly in a further 10 countries.

Of the 51 studies conducted in North America, 38 were conducted in the USA and 12 in Canada, with one involving both these countries.

Of the 38 studies conducted in Asia, seven were conducted in Israel (of which five were the linked GOREN series discussed in §3.3.3 above), and the remainder in 12 further countries[12].

[11] See §7.1 for age criteria for included studies.

[12] Hong Kong is counted here as separate from China.

Of the 40 studies conducted in other areas, seven were conducted in Turkey, six in Australia, five in Poland and no more than four in any other country.

Overall, studies were conducted in 44 countries.

Timing. The earliest period considered by any study was KAPLAN, a prospective study of all UK children born in a specific week in 1958. Four studies started in the 1960s (another birth cohort study in the UK, an American and an Australian cross-sectional study, and an American case-control study). The number of studies starting accelerated, with 16 studies starting in the 1970s, 53 in the 1980s and 107 in the 1990s. All but four of the case-control studies started in 1988 or later. The timing of the study was not stated for 30 studies. For 194 of the studies, the principal publication year was 1990 or later.

Population studied. Most studies were of the general population with no major restrictions – 121 conducted in school settings, 48 in hospital, clinic or routine health check settings and 38 in household or other general settings. Some of these studies imposed further restrictions as detailed in *www.pnlee.co.uk/etsast.htm* [Appendix 14]. Although these were generally of a minor nature, some may have materially affected the representativeness of the population studied. For instance a requirement that the respondent was the biological mother would have reduced the proportion of children in step-families below that for the general population, as well as excluding adopted children, while a restriction on nationality or language spoken may have affected the racial distribution.

One study gave no information about the population considered. The remaining studies involved a variety of special populations – four were restricted to children with a family history of allergy, one to school athletes, one to twins, one to children living on farms and one to infants at high risk of SIDS; one study included a high proportion of travellers' children.

Although no information has been entered on the database regarding response or retention rates, it can be noted that many of the prospective studies based their analysis on children who were alive and could be traced through to the final follow-up. Thus they excluded any children who died during the course of the study, and, depending on the individual study design, may have under-represented children from more mobile families.

Type of controls. Of the 42 case-control studies, 29 used healthy (population) controls. The other 13 studies used other patients as controls, usually from the same hospital or primary care unit as the cases. Thus for two studies (SARRAZ and ROSASV) controls were attending an allergy clinic, while conversely another study (OCONNE) excluded patients with a personal or family history of allergic conditions. A further six studies excluded patients with a history of respiratory disorders. 13 of the studies using population controls excluded children with respiratory or allergic disorders.

Matching factors. The commonest matching factors used in the 42 case-control studies were sex (13 studies) and age (19 studies), while a further nine studies matched for factors such as hospital or location within study area. The only other matching factors used were socio-economic status (SES) and race (two studies each). 22 studies were unmatched.

Respondent. Most commonly (155 studies) information about the ETS exposure was provided by a parent. In 20 studies it was provided by the child, in two studies children above a given age responded in person, while in 24 studies information was provided by both parent and child (including some studies which asked children privately about their own smoking). Of the remaining studies, six obtained information from medical records and 10 obtained it from unspecified household members.

Questionnaire. About one third of the studies used either the ISAAC (Asher et al., 1995), ATS (Ferris, 1978) or WHO (Florey & Leeder, 1982) questionnaires for respiratory symptoms.

Definition of disease outcome – lifetime and incident asthma. Results for lifetime or incident asthma (including prevalent asthma of unspecified timing) were available from 134 principal studies, about two-thirds of the prospective and cross-sectional studies but only about one third of the case-control studies.

The diagnosis was taken from medical records (or was made by a physician in the course of the study design) in 14 studies (including study FERGUS, asthma or wheezy bronchitis, see §7.1). In a further 63 studies a diagnosis made by a physician but reported by the parent and/or child was used. Most of these were simply described as "asthma" or "bronchial asthma," while for a few, the definition of asthma included asthmatic or spastic bronchitis (DOLD, NICOLA), recurrent wheezy bronchitis (KUEHR), or bronchial obstruction verified by a physician (SIGURS). In two studies (BECKET, VONMAF), the unit of study was the family and the outcome was *"at least one child in the family has asthma."*

In the 57 remaining studies, asthma was at least partly based on the parent's or child's own assessment rather than solely on physician diagnosis. In most of these studies this was simply described as "asthma" or "bronchial asthma" (38 studies), "asthma attack" (ANNESI, BENER, KARLAN) or "asthmatic" (VARELA), while in the remaining 15 studies the outcome was defined in terms of a set of symptoms, or a combination of a physician diagnosis and a set of symptoms. These varied considerably, for instance ALDAWO defined asthma as attacks of wheezing with shortness of breath and breathing normal between attacks, while WARKE used a physician diagnosis plus at least two episodes of wheeze precipitated by infection, exercise or allergen exposure. However for some studies, the threshold at which symptoms were accepted as defining asthma was quite low, for instance in POKHAR and ULRIK, "wheeze ever" would have qualified. In one study, ANDRAE, "allergic asthma" was restricted to symptoms occurring on contact with plants or animals.

Details of the diagnostic criteria used are available at *www.pnlee.co.uk/etsast.htm* [Appendix 14].

15 prospective studies recruited mothers of potential subjects in the prenatal period, or infants under 1 year of age. For these studies, analysis of lifetime asthma has been entered on the database as incident asthma, although it could equally well have been described as lifetime prevalence. Four other prospective studies recruited at a later age and presented incidence analysis excluding subjects with baseline history of asthma. Only two of these (RONMA1, MCCON1) also reported results for baseline prevalence (entered as separate studies RONMA3, GILLIL respectively). In study SHERMA, age at onset was used to combine pre-existing asthma at baseline with subsequent incident asthma in a single analysis.

Results entered as lifetime prevalence are in fact restricted to onset after age 2 or age 3 in two studies (FAROOQ and NYSTAD respectively), and are for asthma of unspecified timing in 36 studies.

Definition of disease outcome – current asthma. Results for current (i.e. active) asthma were available from 105 principal studies, including about two-thirds of case-control studies, half of cross-sectional and a third of prospective. In three of the case-control studies, this was restricted to being the first episode of asthma. Details of the diagnostic criteria used are available from *www.pnlee.co.uk/etsast.htm* [Appendix 14]. The diagnosis was taken from medical records (or was made by a physician in the course of the study design) in 22 studies.

In a further 16 studies a diagnosis made by a physician but reported by the parent and/or child was used, while in the 67 remaining studies, asthma was at least partly based on the parent's or child's own assessment rather than solely on physician diagnosis. Many of these latter studies combined "ever diagnosed asthma" with a report of attacks, symptoms or medication use in the last year. In four studies (LOPEZC, HJERN1/HJERN2 and DOTTER) the definition refers to allergic asthma. Comparing with the definitions for lifetime asthma, although some studies had quite a low threshold of symptoms to qualify as asthma (e.g. for MELSOM wheeze in last 12 months would qualify), generally the criteria were stricter, and several studies were restricted to severer asthma (e.g. CALL – subjects presenting at emergency room with acute wheezing; DAIGLE – asthma requiring hospitalization or two primary care visits; HU2 – episode lasting 3+ days; STRACH – 12+ episodes or a severe episode; WEITZ1/WEITZ2 – asthma lasting 3+ months)

In seven of the 11 prospective studies which gave results for current asthma, the current asthma status was repeatedly measured in successive phases of the study. Studies GOLD and BALL (and probably also BERGMA at ages 3-6) combined the repeat measures in a single analysis which dealt appropriately with the non-independent nature of the measures, and thus the results are suitable to include in a meta-analysis. ARSHAD, MILLER, PETERS, TARIQ (and BERGMA at age 7) presented separate analyses each relevant to a single phase. These have been entered on the database as they are potentially of interest in age-specific analyses, but they are not independent. In order to prevent more than one estimate entering a meta-analysis simultaneously, the results from the final follow-up have been marked as principal and others as subsidiary.

In about half the studies (60 studies) current asthma was defined as asthma that had been active in the last year (or in the last two years for another study). A few studies (eight) specified a shorter period, while for the remaining studies, the diagnosis was made in the course of the study design (15 studies) or the timing was unspecified (21 studies).

Availability of alternative disease outcome. Details of the 44 studies from which results are available for alternative asthma definitions are available from *www.pnlee.co.uk/etsast.htm* [Appendix 14]. In some cases, these refer to past asthma, or to exacerbation of asthma which would not have been eligible for the current review. In other cases, the decisions made when choosing which results to enter onto the database can be summarized in the following table.

Study	Preferred	Alternative(s)
ANDRAE	triggered by tree, grass, flowers or furred animals	triggered by birch pollen
ANNES2	ever asthma and wheeze	ever asthma and 4+ speech-limiting attacks or 1+ night-waking attack
BRABIN	asthma	well controlled asthma
CUNNI1	experienced symptoms	taken medication
DUHME2/4	self-completion questionnaire	video questionnaire
EHRLI2	acute or non-acute	acute
FERGUS	Physician-diagnosed asthma or wheezy bronchitis (see §7.1)	asthmatic attack (irrespective of medical treatment)

FORSB1/2/3	treatment by physician	experienced attacks
GILLIL	asthma	taken medication
GOLD	asthma	Physician-diagnosed asthma with wheeze[1]
GORTM1/2	asthma	functionally impairing asthma
HU1	taken medication	emergency hospital treatment
JAAKO	asthma	early onset asthma
KABESC	diagnosis with wheeze in last 12m	diagnosis[1]; atopic asthma; non-atopic asthma; current doctor visit; current medication
KEARNE	asthma	exercise-induced asthma
KUEHR	asthma	allergic asthma
LISTER	asthma	use of health services for asthma
MONTEF	asthma	very severe attack of asthma
NHANE3	asthma	moderate or severe asthma; any hospital visit or recent physician visit for asthma; taken medication
RATAGE	asthma	severe asthma
RONMA1	Physician diagnosed and either symptoms or medication	symptoms or medication; medication
RONMA3	asthma	Physician-diagnosed asthma[1]
SENNHA	bronchial asthma	asthma symptom (frequent night-time irritable cough)
SPENGL	physician diagnosed and symptoms	symptoms
STANHO	episodes labelled as asthma	sub-clinical asthma (wheeze not labelled as asthma)
TARIQ	3+ episodes each lasting 3+ days	medication; nocturnal asthmatic symptoms; atopic and non-atopic asthma
WEITZ1	asthma not cured	taken medication
WOLFO1/2/3	asthma	score based on symptoms

[1] An exception to the usual order of preference was made because results for the usually preferred outcome were much sparser.

The availability of results for wheeze, wheezy bronchitis, “asthma or wheeze” or similar conditions was noted for 96 of the principal studies.

Study size. The distribution of the number of asthma cases was very skew. Where the number of cases was known, for lifetime or incident asthma, it ranged from 6 to 5842, with the median being 168.5, and 21 studies (15%) having over 500 cases. Similarly for current asthma, the range was 8 to 20637, with the median 137 and 12 studies (12%) having over 500 cases. By far the largest study was WANG, conducted in Taiwan with 20637 current asthma cases, followed by STURM in USA with 11378 current asthma cases, MCKEEV in UK with 5842 incident cases and VOLKME in Australia with 3178 lifetime prevalent cases. Other studies with over 1000 cases were conducted in Taiwan (LEE3, 2224), Finland (JAAKK2, 1951), France (ANNES2, 1603), Australia (JENKIN, 1349), Italy (AGABI2, 1306) and USA (NHANE3, 1025). In addition, there were nine other large studies (>1000 subjects) for which the number of asthma cases was unknown.

Exposures. For the exposure types entered on the database (§7.8.1), information about the studies for which RRs have been recorded in the RR database is presented in §9.2. Other exposure types available are described briefly here, with further details available from *www.pnlee.co.uk/etsast.htm* [Appendix 14]. Four studies (ALBA, CHEN2, PONSON and SHIVA) provided results for alternative aspects of household smoking related to whether smoking was anywhere, in the home, or in the presence of the child. AZIZI also gave results for sharing a bedroom with an adult smoker, INFANT for smoking by the babysitter, VARELA for whether the mother was the main active smoker, and GOLD considered respirable particulate matter as equivalent to household smoking. Four studies (BALL, BUTZ, KUEHR and LEEDER) looked at changes in parental smoking habits, while SOYSET looked at duration of parental smoking. Only three studies looked at exposure outside the home (AGUDOT – exposure in means of transport and other public places, BUTZ – exposure in daycare, and PONSON – exposure outside the home at age 1 month).

Active smoking (smoking by the child). Many studies (162, 75%) made no mention of smoking by the child. Although this would be expected in studies of young children, the situation was similar in the 161 studies which included children age 10 and above, with no mention of smoking by the child in 111 (69%). Smokers (identified by means of questionnaire or biochemically) were excluded from analysis in 17 studies, two studies investigated smoking but found that there were no smokers, another reported including only non-smokers without specifying whether some smokers had been omitted, while another three studies assumed that there were no smokers because of the age of the subjects (even though in two, MARTIN and AGABI1, subjects were up to age 12). The remaining 32 studies included smokers in the analysis, with six studies discussing the need to take active smoking into account but having no data available, and with eight either testing formally for its significance or using it as an adjusting factor. In addition, as listed in *www.pnlee.co.uk/etsast.htm* [Appendix 14], 20 studies gave results for active smoking. These results have not been entered on the database.

Confounders. Of the 217 principal studies, 82 (38%) did not adjust for any variable at all in analysis. This percentage was higher for the case-control studies (48%) though some of these will have matched for sex and/or age at the design stage. About half of the studies adjusted for four or more potential confounders, with 29 (13%) adjusting for 10 or more.

Table 9.2 also shows all those variables taken into account. Sex is the commonest, with 93 studies adjusting for it. Other commonly used variables were aspects of family medical history (72 studies), SES or parental education (65), child's medical history (including diet) (61), age (57), cooking, or heating methods (38), household composition (e.g. number of

siblings, single parent) (35), animal contact (32), housing quality or crowding (26), damp or mould in the home (26), and race (23).

Results adjusted for other aspects of passive smoking were available, for *in utero* exposure in 14 studies, for parental smoking (postnatally) in 38 studies and for household smoking in eight studies. Active smoking by the child was used as an adjusting factor in five studies.

Additional confounders were formally considered by the study authors but rejected from analysis (usually in a stepwise multiple logistic regression) in 39 studies.

Other stratifying variables. Only sex, age and race have been considered as stratifying variables in the RR database. However, some studies give details on how the association of passive smoking with asthma varies by level of other stratifying variables. Details of which studies considered other stratifying variables, or presented results for particular subsets of the subjects are available from *www.pnlee.co.uk/etsast.htm* [Appendix 14]. By far the commonest are aspects of medical history (18 studies using the child's medical history and a further 6 using family medical history). Others are location (particularly as related to urban/rural or air pollution), social class, parental education, housing conditions and country of origin.

9.2. THE RELATIVE RISKS

Based on the methods described in §7.8 and §7.9, a total of 1335 RRs were entered on the database, of which 1318 relate to the principal studies and 17 to the subsidiary studies. Among the 217 principal studies, 64 have only one RR, while 11 have over 20 RRs, the highest number being 81 (Table 9.3). The subsidiary studies have up to three RRs.

Table 9.4 gives the distribution of various selected RR characteristics by study type and overall, based on all the 227 studies. Table 9.5 shows how many of the principal studies or their subsidiaries had RRs with selected characteristics, and except where specified otherwise, in the discussion in the rest of this section "study" refers to "a principal study or its subsidiary/ies."

Table 9.3. Relative risks available per study – children

	RRs per study	Number of studies by study type[1]			
		CC	Prosp	CrSec	Total
Principal studies	1	11	6	47	64
	2	10	6	30	46
	3	2	2	12	16
	4	2	6	15	23
	5	2	0	5	7
	6-10	7	6	19	32
	11-20	5	4	9	18
	21-30	1	2	3	6
	>30	2	0	3	5
Subsidiary studies	1	0	1	3	4
	2	1	0	4	5
	3	0	0	1	1

[1] CC = case-control; Prosp = prospective; CrSec = Cross-sectional; see also §9.1.4 "Design."

Table 9.4. Characteristics of the 1335 relative risks – children

Characteristic : Level		Number of RRs by study type[1]				
		CC	Prosp	CrSec	Subsid	Total
Total		352	189	777	17	1335
Sex :	both	350	181	697	17	1245
	male	1	4	42	0	47
	female	1	4	38	0	43
Lowest age in RR :						
	0 - 1	3	13	35	0	51
	2 - 3	0	12	14	0	26
	4 - 5	0	14	24	0	38
	6 - 7	3	17	18	1	39
	8 - 9	0	7	4	0	11
	10 - 11	0	1	0	0	1
	12 - 13	0	0	8	0	8
	14 - 15	0	1	0	0	1
	20 - 21	0	24	0	0	24
	whole study	346	100	674	16	1136
Highest age in RR :						
	0 - 1	0	8	4	0	12
	2 - 3	0	11	10	0	21
	4 - 5	3	17	35	0	55
	6 - 7	0	3	12	0	15
	8 - 9	0	1	0	1	2
	10 - 11	0	5	12	0	17
	12 - 13	3	6	8	0	17
	14 - 15	0	13	0	0	13
	16 - 17	0	1	22	0	23
	22 - 23	0	24	0	0	24
	whole study	346	100	674	16	1136
Race :	whole study	352	181	702	17	1252
	white	0	2	0	0	2
	black	0	0	1	0	1
	white excluding hispanic	0	3	3	0	6
	hispanic white	0	3	2	0	5
	white + black	0	0	66	0	66
	jewish	0	0	2	0	2
	arab	0	0	1	0	1
Time of asthma[2] :	lifetime/incidence	50	125	504	12	691
	current	302	64	273	5	644
Onset :	no	352	93	777	17	1239
	yes	0	96	0	0	96
Odds ratio (onset analysis) :						
	no	-	73	-	-	73
	yes	-	23	-	-	23

Table 9.4. (continued)

Characteristic : Level		Number of RRs by study type[1]				
		CC	Prosp	CrSec	Subsid	Total
Exposure type :	parent smoking	240	156	418	10	824
	parent exposed to ETS	12	2	0	1	15
	household smoking	59	28	267	5	359
	total	5	0	15	0	20
	biochemical	12	0	33	1	46
	in utero × parent	24	3	5	0	32
	in utero × household	0	0	27	0	27
	in utero × biochemical	0	0	12	0	12
Parental exposure - who smoked[3] :						
	not applicable	76	28	354	6	464
	mother (and not father)	8	2	13	0	23
	mother (irrespective of father)	121	93	210	10	434
	father (and not mother)	9	2	20	0	31
	father (irrespective of mother)	95	27	103	1	226
	parents (both)	6	10	15	0	31
	parents (any)	31	18	52	0	101
	mother or father (not both)	6	9	10	0	25
Household exposure - who smoked :						
	not applicable	293	161	483	12	949
	all	48	25	280	5	358
	siblings	0	0	2	0	2
	grandparents	0	0	2	0	2
	grandfather	2	0	0	0	2
	other than parent (and not parents)	0	0	1	0	1
	other than parent (irrespective of parents)	6	0	4	0	10
	other than mother (and not mother)	2	0	3	0	5
	other than mother (irrespective of mother)	1	3	2	0	6
Total exposure - who smoked :						
	not applicable	347	189	762	17	1315
	total NOS	3	0	14	0	17
	home and peers	0	0	1	0	1
	home and day care	2	0	0	0	2
Exposure time :	not applicable	12	0	45	1	58
	before conception	0	0	3	0	3
	during gestations	41	28	62	1	132
	since birth	28	32	62	0	122
	since conception	0	5	6	0	11
	ever	11	5	40	0	56
	ex	10	3	12	0	25
	current	157	25	297	7	486
	unspecified	80	38	216	7	341
	at time of birth/up to 1m	3	11	0	0	14

Table 9.4. (continued)

Characteristic : Level		Number of RRs by study type[1]				
		CC	Prosp	CrSec	Subsid	Total
	during gestation/at 2 m	0	2	0	0	2
	at age 18 months	0	1	0	0	1
	age <6 months	0	0	2	0	2
	age <1	0	0	6	0	6
	age <2	1	0	10	1	12
	age 2 yrs	0	2	0	0	2
	age <3	8	0	2	0	10
	age <5	0	6	0	0	6
	age <6	0	1	0	0	1
	age <7	0	0	1	0	1
	age 13-15 yrs	0	24	0	0	24
	age 9-16 yrs	0	4	0	0	4
	ever, up to 1 yr ago	0	2	0	0	2
	since birth but not current	0	0	12	0	12
	since conception but not current	0	0	1	0	1
	ever but not during pregnancy	1	0	0	0	1
Biochemical measure - where taken from :						
	saliva	1	0	0	0	1
	blood	0	0	42	0	42
	urine	11	0	2	1	14
	hair	0	0	1	0	1
Biochemical marker :						
	cotinine	5	0	44	0	49
	CCR	7	0	1	1	9
Dose-response :	all (not dose-response)	244	156	601	15	1016
	level 1	44	13	65	1	123
	level 2	44	13	65	1	123
	level 3	14	4	16	0	34
	level 4	1	0	2	0	3
	partial	0	1	15	0	16
	per unit dose regression	5	1	6	0	12
	other	0	1	7	0	8
Measure of exposure :						
	yes/no	231	128	577	13	949
	cigarettes/day	80	54	105	0	239
	minutes/day	8	0	0	0	8
	level (semi-quantitative)	0	0	7	3	10
	persons	21	4	38	0	63
	days/month	0	2	5	0	7
	ng/ml	12	0	1	0	13
	mmol/l	0	0	42	0	42
	ng/mg	0	0	1	1	2
	ng/ml/mg	0	0	1	0	1

Table 9.4. (continued)

Characteristic : Level		Number of RRs by study type[1]				
		CC	Prosp	CrSec	Subsid	Total
	cigarettes/day +ve (among smokers only)	0	1	0	0	1
Unexposed – time :						
	not applicable	12	0	45	1	58
	non	261	169	624	16	1070
	never	79	18	85	0	182
	non+other	0	2	23	0	25
Unexposed – source :						
	none (or low)	18	3	78	1	100
	none in household	55	26	289	5	375
	not specified household member	7	2	7	0	16
	neither parent	65	41	106	0	212
	not specified parent	207	117	297	11	632
Combination exposure[4] (*in utero* × in-life exposure vs neither) :						
	combination 0-1	8	1	13	0	22
	combination 1-0	8	1	13	0	22
	combination 1-1	8	1	18	0	27
N adjusted for :	none	216	100	367	9	692
	1	20	14	63	0	97
	2	0	5	22	3	30
	3	1	12	27	2	42
	4-5	11	14	88	2	115
	6-10	22	31	188	1	242
	11+	82	13	22	0	117
Adjusted for						
- sex		108	67	281	6	462
- age		108	23	213	5	349
- race		17	27	145	2	191
- other sources of ETS :						
	none	256	171	699	17	1143
	1	81	18	73	0	172
	2	15	0	5	0	20
- other confounders :						
	none	230	115	411	14	770
	1	6	15	55	0	76
	2	6	2	50	0	58
	3	14	4	49	0	67
	4	3	15	35	0	53
	5	4	5	63	2	74
	6-10	82	31	100	1	214
	11+	7	2	14	0	23
Unadjusted RRs:						
- numbers of cases available		194	73	305	5	577
- numbers of controls/at risk available		194	74	294	5	567
- full 2 × 2 table available		194	73	294	5	566
Adjusted RRs: numbers of cases available		128	42	205	2	377

Table 9.4. (continued)

Characteristic : Level		Number of RRs by study type[1]				
		CC	Prosp	CrSec	Subsid	Total
RR	0.01-1.00	56	31	185	2	274
	1.01-2.00	227	115	466	11	819
	2.01-3.00	26	15	42	0	83
	3.01-4.00	14	2	6	0	22
	4.01-5.00	2	2	1	0	5
	5.01-6.00	3	0	1	0	4
	6.01-7.00	3	0	0	0	3
	7.01-8.00	0	1	1	0	2
	10.01-11.00	0	1	0	0	1
	11.01-12.00	1	0	0	0	1
	median	1.22	1.29	1.21	1.24	1.23
	min	0.04	0.52	0.35	0.16	0.04
	max	11.32	11.00	7.24	1.46	11.32
	missing	20	22	75	4	121
CI available :	no	24	27	121	4	176
	yes	328	162	656	13	1159
Derivation of RR/CI :						
	original	65	64	233	7	369
	RR/CI from numbers	109	50	161	3	323
	RR/CI recalculated from numbers	1	1	19	0	21
	combined exposure levels/sum	69	27	70	0	166
	combined disease levels/sum	19	0	5	0	24
	other combined/sum	3	2	61	0	66
	RR/CI calculated using 0.5 for zero	2	0	0	0	2
	non-significant	21	22	69	4	116
	significant	3	0	16	0	19
	read from graph/chart	0	0	15	0	15
	RR original, CI from p-value	0	0	7	0	7
	combined smoking levels/F&L[5]	44	12	48	1	105
	combined disease levels/F&L[5]	0	0	2	0	2
	adjusted from original RR/CIs by meta	0	1	12	0	13
	combined F&L[5] then adjusted by meta	0	0	5	0	5
	other	16	10	49	2	77
	RR original CI estimated from crude numbers	0	0	4	0	4
	other (with CI estimated from crude numbers)	0	0	1	0	1

[1] CC = case-control; Prosp = prospective; CrSec = Cross-sectional; Subsid = Subsidiary; see also §9.1.4 “Design.”

[2] As defined in the study database (see Table 9.2).

[3] Exceptionally, when the exposure type is “parents exposed to ETS,” this refers to which parent was exposed.

[4] See §7.8.1.

[5] Method of Fry & Lee (2000).

Table 9.5. Relative risk characteristics available from the 217 principal studies (or their subsidiaries) – children

Characteristic	Number of studies[1] by study type[2]			
	CC	Prosp	CrSec	Total
Total	42	32	143	217
Single sex	1	2	10	13
Specific Age	1	15	6	22
Specific Race	0	3	4	7
Lifetime/incidence asthma	13	24	98	135
Current asthma	29	11	65	105
Onset analysis	-	19	-	19
Odds ratio for onset analysis	-	9	-	9
Exposure :				
parent smoking	31	26	87	144
parent exposed to ETS	1	1	1	3
household smoking	22	11	75	108
total	3	0	4	7
biochemical	3	0	3	6
in utero × parent	2	1	2	5
in utero × household	0	0	3	3
in utero × biochemical	0	0	1	1
Parental exposure – who smoked[3] :				
mother only	4	1	5	10
mother (irrespective of father)	20	22	62	104
father only	5	1	7	13
father (irrespective of mother)	13	8	33	54
both parents	4	4	8	16
any parent	13	9	32	54
one parent only	4	3	7	14
Biochemical measure – where taken from :				
saliva	1	0	0	1
blood	0	0	1	1
urine	2	0	2	4
hair	0	0	1	1
Biochemical marker :				
cotinine	3	0	2	5
CCR	1	0	2	3
Exposure time:				
before conception	0	0	2	2
during gestation	9	10	21	40
since birth	3	4	10	17
since conception	0	4	1	5
ex or ever[4]	5	3	13	21
current	11	5	67	83
unspecified	25	10	58	93
at specific age	3	9	10	22
not current	0	0	3	3
Categorical dose-response data	13	6	23	42
Measure of exposure :				
yes/no	40	30	132	202
cigarettes/day	10	9	26	45

minutes/day	1	0	0	1
semi-quantitative	0	0	3	3
persons	5	1	7	13
days/month	0	1	1	2
ng/ml	3	0	1	4
mmol/l	0	0	1	1
ng/mg	0	0	2	2
ng/ml/mg	0	0	1	1
cigarettes/day (among smoking mothers only)	0	1	0	1
Unexposed – time :				
non	42	31	135	208
never	5	3	14	22
non + other	0	1	3	4
Unexposed – source :				
none (or low)	6	2	14	22
none in household	18	10	66	94
not specific household member	6	1	7	14
no parent	13	9	36	58
not specific parent	21	21	62	104
Adjustment for :				
sex	9	20	64	93
age	9	4	45	58
race	3	5	14	22
other ETS exposure	7	4	28	39
other non-ETS variables	19	23	82	124
any adjustment	22	25	89	136
no adjustment	41	26	111	178
Number of cases available	36	16	85	137
RR available	40	27	121	188
CI available	39	26	119	184
Derivation of RR/CI :				
original	15	19	68	102
RR/CI from numbers	32	13	51	96
RR/CI recalculated from numbers	1	1	11	13
combined levels/sum	15	7	25	47
adjustment for zero cell	2	0	0	2
significant/non-significant	14	14	49	77
read from graph/chart	0	0	3	3
CI from p-value, or combined (F&L[5] or meta)	5	6	19	30
other calculation	2	4	17	23
CI estimated from crude numbers	0	0	3	3

[1] Number of principal studies which have (or which have a subsidiary study which has) at least one RR with the characteristic.

[2] CC = case-control; Prosp = prospective; CrSec = Cross-sectional; Subsid = Subsidiary; see also §9.1.4 “Design.”

[3] Exceptionally, when the exposure type is “parents exposed to ETS,” this refers to who was exposed.

[4] Refers to smoker’s lifetime rather than to child’s.

[5] Method of Fry & Lee (2000).

Sex. Only 11 studies give any results for males and females separately, in addition to the two studies which included males only. The great majority of RRs (1245, 93%) are for sexes combined

Age. 1136 RRs refer to the full age range of the study. The 199 RRs which refer to specific age groups are from 22 studies. 24 RRs from seven of these studies are marked as subsidiary RRs because they refer to interim follow-up phases of a prospective study.

Race. 1252 RRs refer to all races (within the scope of the study). The 83 RRs where a restriction applied come from four studies where the results were stratified on race (whites and blacks in FREEM1, non-hispanic and hispanic white in BECKET and DODGE, and Jewish and Arab in KIVITY) and three studies which gave results restricted to a subset (whites only in GOLD and TAYLOR, and whites and blacks in NHANE3).

Asthma type. The RRs refer about equally to lifetime (595) or to current (644) asthma prevalence. The remaining 96 refer to incidence, with 23 of these being odds ratios rather than RRs. The majority of RRs from case-control studies (86%) refer to current asthma, while the majority from cross-sectional studies (65%) refer to lifetime asthma.

ETS exposure (questionnaire assessed). As described earlier, the term "ETS exposure" is used even though, in some studies, it may refer to smoking by parents or other household members irrespective of whether they smoked in the presence of the child. Over half the RRs (814) refer to parental smoking, and these come from 144 studies. Five of these studies have an additional 32 RRs referring to combinations of parental smoking (since birth) × *in utero* exposure. The most common are for maternal smoking (434 RRs from 104 studies irrespective of father's smoking, and 23 RRs from 10 studies for mother only), followed by paternal smoking (226 RRs from 54 studies irrespective of mother's smoking and 31 from 13 studies for father only). 101 RRs from 54 studies refer to any parental smoking. Only 15 RRs from three studies refer to parental ETS exposure (i.e. passive smoking by a parent).

A further 359 RRs from 108 studies refer to household exposure, and 27 RRs from three of these studies to combinations of household exposure × *in utero* exposure. Overwhelmingly these refer to all household members, with just 28 RRs referring to specific family members. Only 20 RRs from seven studies refer to total ETS exposure.

The most frequent timing of the ETS exposure is current, with 486 (36%) RRs from 83 studies, followed by unspecified timing with 341 (26%) RRs from 93 studies. There are 132 RRs from 40 studies which refer to *in utero* exposure (regardless of in-life exposure). Results for exposure during the child's lifetime generally are given in 122 RRs from 17 studies, with a further 11 RRs (five studies) referring to lifetime and/or *in utero*, 85 RRs (22 studies) referring to a specific time in the child's life[13] and 13 RRs (three studies) to lifetime but not current exposure. 21 studies give results referring to whether the parent was an ever or ex-smoker (irrespective of how this related to the child's lifetime), with 58 and 25 RRs respectively, and there is one RR for maternal ever smoking but not smoking during pregnancy. Three RRs from two studies refer to smoking before the child's conception.

For most RRs (1070, 80%), the denominator group comprises all those not exposed at the defined exposure time for the numerator. In 25 RRs some longer period is unexposed (e.g. if the numerator exposure group is "currently exposed" then the denominator group may be "no exposure in lifetime"). In 182 RRs from 22 studies, the denominator group is those whose

[13] Including exposure at baseline in some prospective studies.

parents (or rarely, other household members) have never smoked (not even before the child's lifetime).

ETS exposure (biochemically assessed). Most of the results for biochemically assessed exposure come from study NHANE3 (42 RRs, of which 12 are for combinations of biochemically assessed exposure × *in utero* exposure), and refer to serum cotinine. The remaining 16 results refer either to cotinine or CCR, in saliva (CLARK), urine (EHRLI2, KNIGHT, SPIEKE, WILLE1), or hair (also KNIGHT).

Dose-response. 283 RRs from 42 studies refer to categories by amount of passive smoke exposures, comprising 89 sets of 2 categories, 31 sets of 3 categories and 3 sets of 4 categories. Of these sets, 55 are for parental smoking, four for parental ETS, 50 for household smoking, two for total exposure and 12 for biochemically assessed exposure. Most sets are based on numbers of cigarettes per day, including all the parental and about half the household sets. Most of the others are based on number of persons, with a few based on duration or frequency of exposure. In addition one RR refers to heavy vs light maternal smoking (i.e. among maternal smokers only – study XU), and three studies (NHANE3, WEITZ1, KABESC) gave results only for heavy exposure vs unexposed (i.e. omitting the corresponding results for light exposure).

20 RRs hold results regarding the dose-response relationship which could not be expressed in the usual categorical format (Table 9.6). These comprise 12 results from six studies expressed as risk per unit dose (CHINN and SOMERV – parental cigarettes/day; DIJKST and PONSON – household cigarettes/day; EHRLI1 – household smokers; EHRLI2 – urinary cotinine), four results from study KNIGHT where the mean exposure (household cigarettes/day or cotinine) was given for cases and controls together with a p-value, one result from study KASPER expressed as a correlation between asthma prevalence and household cigarettes/day, and three results where the dose-response (household or parental cigarettes/day) was simply stated to be significant (ALFRA1, TARIQ) or non-significant (SCHMIT).

Adjustment. 643 (48%) RRs have some adjustment. Of sexes-combined RRs, 37% are adjusted for sex. Among the adjusted RRs, 54% are adjusted for age, 30% for race, 30% for other passive smoking exposure and 88% for other factors. The adjusted RRs come from 136 studies (78% of prospective studies, 62% of cross-sectional studies and 52% of case-control studies). 39 studies only have adjusted RRs.

2 × 2 table. Among the unadjusted RRs, the full 2 × 2 table is available for 566 (82%) RRs and the numbers of cases for another one. Among the adjusted RRs, the numbers of cases is available for 377 (59%). There are 80 studies which do not have the numbers of cases for any RR.

RR and CI. 121 RRs have no values for the RR or CI, having only a statement of significance[14] (12) or non-significance (109). A further 55 lack a CI, and of these seven are stated to be significant and seven non-significant. There are 33 studies which have no complete RR/CIs.

The RR values range from 0.04 to 11.32.

The centrality of the RR in the CI was checked as described in §7.9. The value of C was outside the range 0.95 - 1.05 for 51 RRs. For all but four of these, C was in the range

[14] These probably all refer to a significant increase, although this was not always explicitly stated in the original paper.

0.80 - 1.25 and the CI was either given originally to only one decimal place or was read from a graph, so the difference is probably due to rounding error. The remaining five RRs are shown in Table 9.7 part A.

Table 9.6. Other dose-response results – children

Study	Asthma	Exposure	Adjusted	Results
ALFRA1	lifetime	any parent	no	number of cigarettes, significant p<0.001
CHINN	current	any parent, current	yes	RR per cigarette is 1.001 (0.991-1.011)
DIJKST	current	household, current	yes	RR per 10 cigarettes is 0.93 (CI not given)
EHRLI1	current	household, current	yes	RR per household smoker is 1.07 (0.91-1.25)
EHRLI2	lifetime	urinary cotinine	no	RR per ng/ml is 1.009 (1.003-1.015)
EHRLI2	lifetime	urinary CCR	no	RR per ng/ml is 1.004 (0.999-1.008)
EHRLI2	lifetime	urinary cotinine	yes	RR per ng/ml is 1.009 (1.003-1.016)
EHRLI2	lifetime	urinary CCR	yes	RR per ng/ml is 1.004 (0.999-1.009)
KASPER	lifetime	household, current	no	number of cigarettes (9 categories), correlation R=0.794, p=0.011. The authors commented that the probability of asthma was fairly constant in the range 0-40 cigarettes, then rose fairly quickly
KNIGHT	current	household	no	mean cigarettes 7.4 (asthmatic) vs 11.2 (non-asthmatic), p=0.144
KNIGHT	current	urinary cotinine	no	mean (ng/ml) 29.9 (asthmatic) vs 39.4 (non-asthmatic), p=0.23
KNIGHT	current	urinary CCR	no	mean (ng/ml/mg) 47.1 (asthmatic) vs 62.6 (non-asthmatic), p=0.2
KNIGHT	current	hair cotinine	no	mean (ng/ml) 0.696 (asthmatic) vs 0.386 (non-asthmatic), p=0.0001
PONSON	incidence	household, at birth	yes	RR per 20 cigarettes is 1.04 (0.99-1.10)
SCHMIT	current	any parent	no	number of cigarettes, non-significant
SOMERV	current	any parent	yes	RR per cigarette is 0.995 (0.972-1.019) for boys, and 1.026 (1.001-1.053) for girls
SOMERV	current	any parent	yes[1]	RR per cigarette is 0.986 (0.967-1.006) for boys and 1.018 (0.998-1.038) for girls
TARIQ	current	household	no	non-significant. Prevalence of asthma was 18.3% for smoking ≤ 5 cigs per day, and 17.1% for smoking >20.

[1] age only.

Table 9.7. Relative risks with apparent errors – children

A – Confidence interval is non-symmetrical[1]

Study	RR no.	Asthma	Exposure	RR/CI[2]			C[3]	Centre of CI[4]
				RR	LCL	UCL		
ALFRA1	2	lifetime	parent	1.51	1.04	2.37	0.925	1.57
NHANE3	57	current	biochemical	1.7	0.7	7.3	0.566	2.26
POKHAR	2	lifetime	household	3.33	1.85	7.65	0.784	3.76
SHAMS2	1	lifetime	parent	1.18	0.94	1.24	1.195	1.08
TARIQ	16	current	parent	1.2	0.3	2.7	1.778	0.90

B –Number of cases implied by confidence interval is greater than actual number of cases (Case-control and cross-sectional studies)

Study	RR no.	Asthma	Exposure	No.of cases	RR/CI[2]			Min. cases[5]	Ratio[6]
					RR	LCL	UCL		
ALFRA1	1	lifetime	parent	106	1.32	1.01	1.72	216.9	2.05
ALFRA2	1	lifetime	parent	134	1.08	0.83	1.41	218.9	1.63
ANNES2	3	current	parent	735	1.0	0.9	1.2	742.7	1.01
FARBE2	2	lifetime	parent	225[7]	1.51	1.17	1.96	230.9	1.03
FLYNN1	1	lifetime	household	136	1.26	0.95	1.68	189.1	1.39
HJERN1	13	current	parent	119	0.72	0.52	1.01[8]	139.5	1.17
HJERN2	13	current	parent	78	0.94	0.62	1.43[8]	88.0	1.13
KENDIR	1	lifetime	household	304	1.41	1.16	1.72	396.2	1.30
LEE1	1	current	household	774[7]	1.37	1.24	1.51	1583.9	2.05
LEE2	1	current	household	148[7]	0.99	0.87	1.13	899.1	6.07
RIBEIR	1	current	parent	25[7]	1.20	0.59	2.41	31.0	1.24
RONCH1	7	lifetime	household	123	1.40	1.02	1.91[9]	156.2	1.27
SHAMS2	1	lifetime	parent	669	1.18	0.94	1.24	801.2	1.20
STAZI	1	lifetime	parent	6	3.3	1.0	10.6	11.0	1.84

C – Number of subjects implied by confidence interval is greater than actual number of subjects (Case-control and cross-sectional studies)

Study	RR no.	Asthma	Exposure	No. of subjects	RR/CI[2]			Min. subjects[10]	Ratio[11]
					RR	LCL	UCL		
POKHAR	2	lifetime	household	120	3.33	1.85	7.65	122.0	1.02
SHAMS2	1	lifetime	parent	3000	1.18	0.94	1.24	3204.6	1.07

[1] Only those which cannot be explained by rounding error are shown, see text.
[2] As given originally, except where indicated otherwise.
[3] Calculated as (RR × RR) / (UCL × LCL)
[4] Calculated as √(LCL × UCL)
[5] Calculated from formula 9 of Lee (1999a).
[6] Ratio of minimum cases to number of cases.
[7] There is a known problem with the value for the number of cases – see *www.pnlee.co.uk/etsast.htm* [Appendix 13].
[8] Estimated by the method of Fry & Lee (2000) based on RR/CIs originally given to 1 decimal place.
[9] Estimated from regression coefficient and SE.
[10] Calculated from formula 7 of Lee (1999a).
[11] Ratio of minimum subjects to number of subjects.

For case-control and cross-sectional studies, the minimum number of cases and the total number of subjects implied by the CI (Lee, 1999a) were compared with the actual numbers, as entered in the study database. The RRs where this showed a problem are listed in Table 9.7 parts B and C. In many, the difference is associated with a problem in establishing the number of cases which was noted on data entry, or may be due to rounding error. However in some RRs, the CI implies about twice the number of cases than actually reported, without any apparent explanation (ALFRA1, STAZI).

For analyses of prospective studies, the equivalent check on the number of cases is only approximate (see formula 16 of Lee, 1999a) and there were no RRs where a gross difference was seen, the largest ratio of implied to actual cases being 1.8 (data not shown).

Derivation method. 692 (52%) RRs are either as given originally, were calculated directly from the numbers in the 2×2 table, or were calculated adjusting for strata from the numbers in the $2 \times 2 \times n$ table. For a further 21 RRs where both the 2×2 table and the RR and CI were originally available, the RR and CI were recalculated because of a discrepancy and 256 were calculated after summing categories to obtain a 2×2 table. Just two RRs were calculated using a zero cell correction (both from case-control studies, one having no exposed cases and the other no exposed controls). 15 RRs were read from graphs or charts and 20 RRs were calculated by other straightforward methods (CI from p-value, combining from independent estimates). The method for combining non-independent estimates (Fry & Lee, 2000) was used for 107 RRs. Other methods, or combinations of methods (but not estimation of adjusted CIs from crude numbers) were used for 82 RRs. The remaining five RRs involved estimation of the CI from crude numbers (from studies BURCHF, ANDRAE and KUHR, all of which also have RRs with other types of estimation).

9.3. THE META-ANALYSES

9.3.1. Introduction

The process of selecting which RRs to include in an analysis based on “preferences” and the combining of the RRs (Fleiss & Gross, 1991) were as described in §7.10.1 and §7.10.2.

The tables relate to five broad types of meta-analysis, as follows:

C) Exposure in the child’s lifetime (irrespective of *in utero* exposure)
D) Amount of exposure in life
E) Exposure *in utero* (irrespective of in-life exposure)
F) Amount of exposure *in utero*
G) Joint effects of *in utero* and in-life exposure

Results from tables C, D, E, F and G are discussed in turn in §9.3.2 - §9.3.6, the tables themselves being included at the end of this chapter.

Table 9.8. Key analyses for in-life exposure – children

Table	Definition of asthma outcome	Source of ETS exposure	Time of ETS exposure	Definition of non-exposure
C1	Lifetime	Total (or nearest equivalent)	General	Most
C3	Current	Total (or nearest equivalent)	General	Most
C5	Lifetime	Parent	General	Most
C7	Current	Parent	General	Most
C25	Lifetime/current	Total (or nearest equivalent)	General	Most
C26	Lifetime/current	Parent	General	Most
C31	Lifetime-physician	Total (or nearest equivalent)	General	Most
C33	Current-physician	Total (or nearest equivalent)	General	Most
C41	Lifetime	Both parents	General	Most
C43	Current	Both parents	General	Most
C45	Lifetime	Mother/mother only	General	Most
C47	Current	Mother/mother only	General	Most
C53	Lifetime	Father/father only	General	Most
C55	Current	Father/father only	General	Most
C65	Lifetime	Not mother	General	Most
C67	Current	Not mother	General	Most
C69	Lifetime	Total (or nearest equivalent)	Discontinued	Most
C70	Current	Total (or nearest equivalent)	Discontinued	Most

Terms are defined in §7.10.5, as are alternative terms for outcome ("current/lifetime" and "onset"), source of ETS exposure ("mother only," "father only" and "household member other than parent"), time of exposure ("recent" and "earliest") and definition of non-exposure ("least") which are used in the variant analyses.

The layout of the tables is as described in §7.10.3. Briefly, each meta-analysis table has a preamble followed by results of the "adjusted" data. The preamble describes the restrictions on the data included, the order of preference for selecting RRs to be included and a short description of the contents of the table. Appendix Tables C-G giving extended versions of the analyses are available at *www.pnlee.co.uk/etsast.htm*. They include a cover page and 8 sections – the cover page and section 3 are the same as the Tables presented here. Sections 1-2 give more of the "adjusted analysis," sections 4-6 relate to the "unadjusted analysis" and sections 7 and 8 give additional information related to studies and RRs excluded from the meta-analysis. Thus the reader who wishes only to see the "key" meta-analysis estimates need refer only to the Tables, but the more interested reader who wishes to see full details of the individual RRs contributing to the estimates, or additional "non-key" analyses, should refer to the corresponding Appendix Tables. The two sets of output always correspond directly.

Chapter 7 also provides information on some general restrictions to the analyses (in §7.10.4), the various ways outcome and exposure are defined (§7.10.5), the various factors considered in the analysis (§7.10.6), how meta-analyses by amount of exposure (§7.10.7) and by age (§7.10.8) are conducted, and certain conventions used in presenting the findings in this chapter (7.10.9).

9.3.2. Risk from Exposure in the Child's Lifetime (Irrespective of *In Utero* Exposure) – Table C and Appendix Table C

All analyses considered in §9.3.2 and presented in Table C (and presented in more detail in Appendix Table C) have the restriction, in addition to those already defined in §7.10.4, that the RRs are selected for exposure in the child's lifetime if available, otherwise for ever smoking by a parent or household member and rarely, where no other exposure period is available, for exposure in life and/or *in utero*. "Ever smoking" by a parent or household member is irrespective of whether this coincided with the child's life. Exposure of timing unspecified in the source paper is also included. "Exposure" may be defined as parents or household members smoking, irrespective of whether this is actually in the presence of the child.

In all, 70 meta-analyses were carried out, of which 18 are key analyses presented in Table C. The key analyses are as shown in Table 9.8. The other 52 variant analyses are presented only in Appendix Table C, and their numbering will become apparent later in §9.3.2.

Table C1: Lifetime Asthma/Total Exposure

Table C1 presents meta-analyses relating lifetime asthma to the nearest equivalent of total ETS exposure. As in all analyses in Table C, the results relate to exposure during the child's lifetime (or nearest equivalent) and the RRs relate to the exposed/unexposed comparison, and are not concerned with the extent of the exposure.

Figure 9.1 presents the 110 RRs from the 104 studies included in the adjusted meta-analysis in Table C1. 87 are greater than 1.00, 34 are statistically significantly positive ($p<0.05$) and two are statistically significantly negative. Overall, there is a highly significant ($p<0.001$) increased risk of lifetime asthma in relation to total exposure, with the RR 1.20 (95% CI 1.17-1.23) for the fixed effects analysis and 1.23 (1.17-1.29) for the random effects analysis. In the unadjusted analysis (i.e. using RRs unadjusted for covariates where possible) the estimates are 1.21 (1.18-1.24) for the fixed effects analysis and 1.24 (1.18-1.31) for the random effects analysis.

In the following text we restrict attention to the adjusted analyses. Egger's test shows no clear evidence of publication bias ($0.05<p<0.1$). The heterogeneity chisquared is 293.19 on 109 d.f. ($p<0.001$). The largest contributor to the excess of the chisquared over the degrees of freedom is the large LEE3 study in Taiwan, which has a Q_s value of 71.64 based on a significantly low RR of 0.82 (0.76-0.90). Other studies with relatively high Q_s values include FREEM1, where the value of 30.76 comes from a significantly high RR of 2.10 (1.72-2.56) and the KERSHA study which has a Q_s of 10.74 from a significantly high RR of 3.12 (1.76-5.54). The other study with a statistically significant negative RR is STANHO where the RR is 0.40 (0.16-0.97), and the Q_s 5.89. The study with the largest weight is MCKEEV, which reports a RR of 1.31 (1.24-1.39) based on 3697 cases. Its weight, 1119, is twice as high as that for LEE3, 514, and more than five times larger than in any other study, and is 19% of the total weight of 6027.

The paragraphs below consider variations in RR by the factors given in §7.10.6. Before doing so it should be made clear that none of these factors on their own explained the heterogeneity of the data. For a number of the factors the ratio of the chisquared between factor levels to its d.f., though nominally significant, is little or no more than might be

expected bearing in mind the ratio of 2.7 for the overall data. Accordingly, attention is drawn mainly to variations between levels with a particularly high ratio, and where the variation by factor level remains evident in the random effects estimates. Attention is also drawn to levels of a factor where the excess risk evident in the total data is not apparent.

Sex. Remarkably, 97 of the 104 studies report results only for the sexes combined, where the RR is 1.20 (1.17-1.23). RRs for the studies reporting results only for male children (1.18, 1.03-1.36) or female children (1.06, 0.90-1.23) do not differ significantly from the estimate for sexes combined.

Location. RR estimates vary by continent ($p<0.001$). However they are generally above 1.00 for each continent and are also elevated in all the six regions considered within Europe. Exceptionally, the fixed effects estimate for Asia is below 1.00 (0.96, 0.90-1.03), due mainly to the large contribution of the LEE3 study, the random effects estimate for Asia being elevated (1.21, 1.02-1.43). Within Asia there is also some variation ($p=0.001$), with RRs significantly elevated in Central and South Eastern Asian studies and in Middle Eastern studies, but significantly reduced ($p<0.001$) in the six Far Eastern studies (0.87, 0.81-0.94). Unlike for Asia as a whole, the random effects estimate for Far East Asia is less than 1.0, though not significant (0.96, 0.83-1.12).

Timing. Significantly increased RRs, between 1.1 and 1.3, are seen in all periods studied, whether classified by year of the start of the study or year of publication, with no real evidence of heterogeneity.

Study type. RR estimates are elevated in the 74 cross-sectional studies (1.16, 1.13-1.20), the 17 prospective studies (1.27, 1.21-1.33) and the 13 case-control studies (1.25, 1.08-1.46).

Age of children. RRs are also increased in all the categories used to classify the studies according to the highest age considered.

Population setting. The fixed effects analyses show heterogeneity ($p<0.01$) according to the setting of the study. For the three types most commonly seen, RRs are highest for medical setting studies (1.29, 1.23-1.35), lowest for school studies (1.15, 1.11-1.19), and intermediate for general population studies (1.22, 1.14-1.31). However the difference is less marked in the random effects analyses.

Respondent for ETS exposure. There is highly significant heterogeneity here (χ^2_{het} = 29.65 on 3 d.f., $p<0.001$[15]) due to the lack of association of lifetime asthma with total ETS exposure seen in the 10 studies where the child was the respondent (1.03, 0.95-1.11). Where the respondent was the parent (1.17, 1.13-1.21), where the data came from medical records (1.31, 1.24-1.38) or where it came from mixed or other sources (1.27, 1.20-1.35) a significant elevation of risk is clearly seen.

Child smokers. There is some heterogeneity ($p<0.05$), with the RR estimate lower where studies specifically did not include children who smoked (1.10, 1.02-1.18) than in those where smokers had been included (1.26, 1.15-1.38) or where the question had been ignored (1.21, 1.17-1.24). The pattern is evident in both the fixed and random effects analyses.

Physician diagnosis. There is little evidence of heterogeneity of the RR according to whether the diagnosis of asthma was made by the physician.

[15] Referred to as Between Chi on the output.

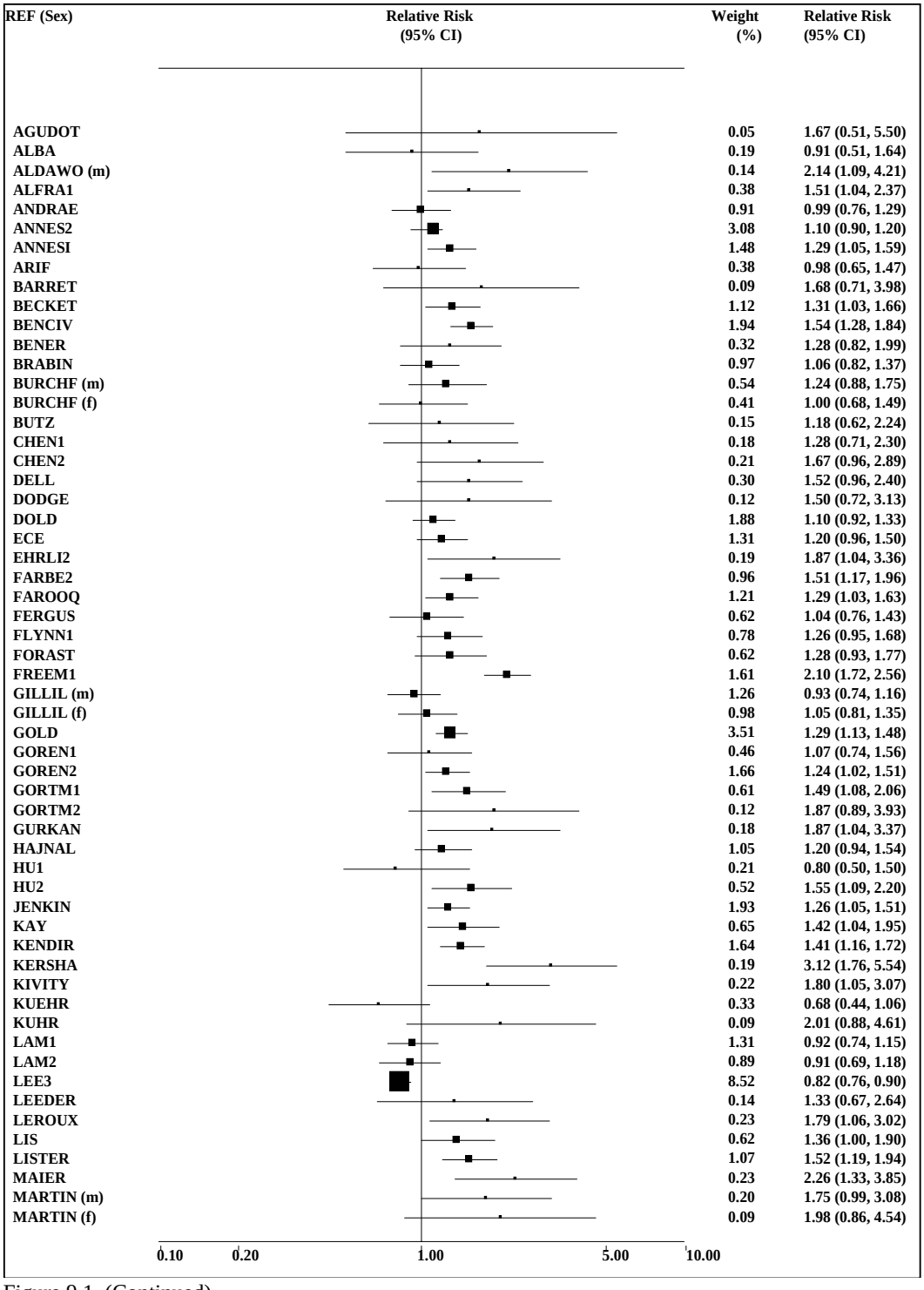

Figure 9.1. (Continued)

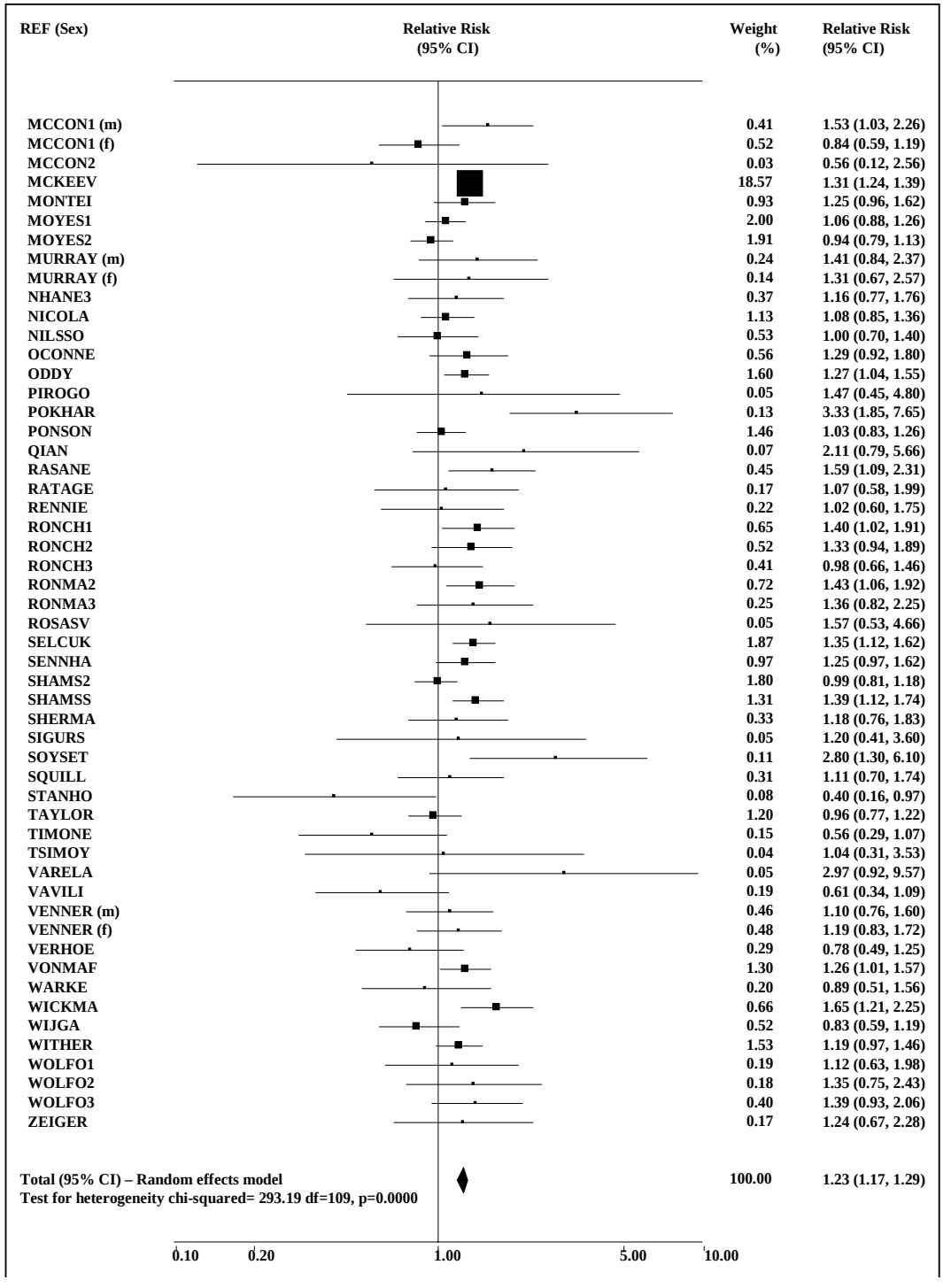

Figure 9.1. Forest plot for lifetime asthma and total in-life exposure – children[1].

[1] Asthma outcome: lifetime; source of ETS exposure: total (or nearest equivalent); time of ETS exposure: general; definition of non-exposure: most; these terms are defined in §7.10.5. Data as used in Table C1. The RRs used are adjusted for covariates where adjusted data are available.

Respondent for diagnosis. There is highly significant evidence of heterogeneity here (χ^2_{het} = 34.77 on 3 d.f., p<0.001). As for respondent for exposure (see above) this is due to the lack of association seen where the child answered the questions concerning the diagnosis (1.04, 0.97-1.12). Where the parent answered the question (1.17, 1.13-1.21), the information was obtained from medical records (1.30, 1.23-1.37) or the information came from mixed sources (1.38, 1.26-1.50) a significant elevation in risk is seen. Note that though the parent or the child answered the question, the actual diagnosis may still have been made by a physician.

Questionnaire for symptoms. There is significant heterogeneity according to use of standard questionnaires to obtain details of symptoms. While there was an elevated risk of 1.25 (1.15-1.37) for studies using the ATS questionnaire and of 1.28 (1.24-1.32) for studies using neither ATS nor ISAAC, there was no elevation when the ISAAC questionnaire was used (1.03, 0.99-1.08). Partly this was due to the large LEE3 study with a low RR using ISAAC, though random effects estimates were also lowest for ISAAC.

Analysis type. RRs are clearly elevated whether onset or prevalence analysis was used.

Size of study. There is no marked heterogeneity by study size, with a significant elevation being seen in studies of 1-50, 51-100, 101-200 or 201+ cases of asthma, although there is some evidence of a decreasing trend (p<0.01)[16] with RRs of 1.53, 1.41, 1.20 and 1.18 respectively.

Adjustment for confounding variables. A variety of RR comparisons were made, according to whether the study took into account specific factors as potential confounders, to whether the RR itself was adjusted for specific factors, or to the number of factors the RR was adjusted for. Although some show nominally significant evidence of heterogeneity, this seems mainly due to the low RR in the LEE3 study, and RR estimates are generally in the range 1.2 to 1.3. The sole exception is that in those studies that adjusted for *in utero* exposure there is no significant increase in risk whether using fixed effects meta-analysis (1.03, 0.88-1.19) or random effect meta-analysis (1.07, 0.84-1.39). The question of the relative importance of *in utero* and in-life exposure is considered in more detail in §9.3.6.

Source of exposure. The choice of total exposure index involves the following order of preference: 1. total-biochemical, 2. total-questionnaire, 3. any household member, 4. any/unspecified parent, 5. mother regardless of father, 6. mother only, 7. father regardless of mother and 8. father only. For the analysis treating source of exposure as a factor level, preferences 5 and 6 (mother) and preferences 7 and 8 (father) are combined. There is highly significant heterogeneity by source of exposure (χ^2_{het} = 41.91 on 5 d.f., p<0.001). For most of the 104 studies, the preferencing led to choice of any household member (45 studies), any parent (20 studies) or mother (30 studies) as the source of exposure, with total-biochemical data selected for only two studies, total-questionnaire exposure selected for only five studies, and smoking by the father selected for only two studies. Given the small number of studies where total exposure is defined based on these last three sources, the heterogeneity mainly arises because RR estimates are higher when the mother is the source (1.31, 1.26-1.36) than when any parent is (1.21, 1.12-1.33) or any household member is (1.09, 1.05-1.14).

Time of exposure. Risks are significantly elevated regardless of the time of exposure category chosen by the preferencing. The most common categories are current exposure (1.28, 1.21-1.35, n=33 RRs), during child's lifetime or ever (1.24, 1.19-1.30, n=25) and

[16] Based on additional analysis (full details not shown) using trend coefficients of 1, 2, 3, 4.

unspecified time (1.10, 1.05-1.26, n=39). The lower estimate for unspecified time is the main contributor to the heterogeneity (p<0.001), arising partly because of the contribution of the low RR in the LEE3 study.

Unexposed group – source of exposure. There is significant heterogeneity (χ^2_{het} = 39.52 on 2 d.f., p<0.001) by the definition of the unexposed group, but this largely reflects the findings for "source of exposure" given above. Thus the largest RR is for "not the specified parent" (1.31, 1.26-1.36), based on essentially the same individual RRs for mother reported above. This is because for all 30 studies which reported results for mother smoking, the unexposed group selected by the preferencing used in Table C1 is virtually always "not mother" and these 30 studies form all but one of the studies selected for "not the specified parent," the other being study QIAN, where the risk estimate is for "father" vs "not father."

Unexposed group – time of exposure. There is some heterogeneity by the definition of the unexposed time, with RRs higher for never (1.30, 1.23-1.36) than for non (1.16, 1.13-1.20).

Note that additional analysis in §9.3.2 will investigate further and more completely the role of the definition of source of exposure, time of exposure, and the unexposed group. The results presented in Table C1 are incomplete in the sense that additional data are available for many of the levels considered there. For example, only three RRs from two studies are included for father smoking in Table C1 as in nearly all cases where data for father smoking are available, data for mother smoking, and possibly other indices of exposure higher up the preference list for total exposure, are chosen instead.

Derivation of RR (CI). There is heterogeneity (χ^2_{het} = 32.30 on 3 d.f., p<0.001) according to whether the RR was available directly in the source publication (1.26, 1.21-1.32, n=41), had been calculated directly from numbers in the 2 × 2 table (1.08, 1.03-1.13, n=35), had been calculated by summing numbers over strata (1.10, 0.99-1.22, n=14) or more complex methods had been used (1.26, 1.21-1.32, n=20).

Overall, the main sources of heterogeneity appear to be the lack of association seen in Far Eastern studies (China, Japan, Hong Kong, Taiwan and Korea), the lack of association seen in studies where the child reported the data on ETS exposure or asthma diagnosis, the lower RRs seen in studies which specifically did not include children who smoked in the analysis, the lack of association seen in studies that adjusted for *in utero* exposure and the higher RRs where the data related to smoking by the mother.

Alternative RRs which would have been selected as higher preference except that they were incompletely reported are available for 10 studies. In three of these (ALFRA1[17], LISTER, RASANE) the incomplete RR is non-significant, whereas the included RR is significant. Otherwise the incomplete and the included RRs are either both significant or both non-significant.

A further 23 studies provide only incomplete data (25 RRs). For three studies (DEBENE, GORENE, STERN2) the RRs are greater than 1.00 and significant. Study RUDNIK gives two RRs (for ages 11-13 and 14-16) greater than 1.00 (1.09 and 1.43) with significance not stated, and one (for age 8-10) less than 1.00 (0.74) with significance not stated. The remaining 19 studies report non-significant RRs. This indicates a lower proportion of significantly elevated RRs than in the included studies (probably 3/25 = 12% and at most 5/25

[17] For Study ALFRA1, the CI was omitted from the database because of concerns about the quality of statistical analyses, see §9.1.3

= 20%, as compared with 34/110 = 31%). The results considered in this and the previous paragraph both indicate that the RR estimates derived in Table C1 are to some extent overestimated due to less complete reporting of non-significant results.

Table C3: Current Asthma/Total Exposure

Whereas Table C1 considers meta-analysis results for lifetime asthma, Table C3 considers results for current asthma, other preferences being identical.

Figure 9.2 presents the 87 RRs included in the adjusted meta-analyses in Table C3. These come from 17 studies which contributed to the meta-analyses in §3.2 and 68 studies which did not provide data for lifetime asthma. 58 of the 87 RRs are greater than 1.00. 23 are statistically significantly positive (at $p<0.05$) and none are significantly negative. Overall there is a highly significant ($p<0.001$) increased risk of current asthma in relation to total exposure, with the RR 1.17 (1.15-1.20) for the fixed effects analysis and 1.20 (1.13-1.27) for the random effects analysis. In the unadjusted analysis (Appendix Table C3) the estimates are 1.20 (1.18-1.23) for the fixed effects analysis and 1.22 (1.13-1.31) for the random effects analysis. All these four RR estimates are slightly lower than the corresponding estimates for lifetime asthma. Again we restrict attention below to the adjusted analyses. There is no evidence of publication bias from Egger's test. The heterogeneity chisquared is 294.93 on 86 d.f. ($p<0.001$), a somewhat greater chisquared per d.f., 3.4, than seen in Table C1. The studies contributing most to the heterogeneity are STURM, which has a Q_s of 81.51 based on a high RR of 1.59 (1.49-1.70), WANG, which has a Q_s of 25.47 based on a low RR of 1.08 (1.05-1.12), and DOTTER which has a Q_s for the sexes combined of 11.57 based on RR estimates of 0.50 (0.30-1.00) for males and 0.50 (0.20-1.10) for females. The study with by far the largest weight is WANG. Its weight is 3689 of a total of 7867, or 47% of the total. STURM also has a large weight, of 884.

Interpretation of the analyses studying variation in risk by level of the various factors is complicated by the very large weight and low risk estimate for the WANG study and the large weight and high risk estimate for the STURM study. Risk estimates for factor levels that include these studies tend to be strongly affected by them. However, bearing in mind these reservations, there seems to be evidence that the RR:

- varies markedly between region of Asia, being highest in those in the Central/South East region and lowest in the Far Eastern studies;
- is not elevated in studies starting early (1970-79) or published early (<1990);
- is higher in case-control studies than in prospective or cross-sectional studies;
- is higher where the child is aged 0-9 years;
- is lower in those studies which took into account smoking by the child;
- is higher if the asthma diagnosis came directly from medical records;
- is higher if the study adjusted for aspects of the child's medical history; and
- is higher if the RR was adjusted for other sources of ETS exposure.

These comparisons are all evident whether fixed or random effects RR estimates are compared. There are a number of other statistically significant sources of heterogeneity indicated in Table C3 but these are not seen in the random effects analysis and are considered less reliable.

Alternative RRs which would have been selected as higher preference except that they were incompletely reported are available for 7 studies. In one study (ADDOYO, adjusted) the incomplete RR is non-significant, whereas that included is significant. In two studies (PALMIE, adjusted; STRACH, exposure as newborn), the opposite is true. Otherwise the incomplete and the included RR are either both significant or both non-significant.

A further 11 studies provide only incomplete data – one (MELIA) is significant but the RR is not stated; one (DEKOK) is greater than 1.00 and one (STERN2) less than 1.00, both being not significant; and the remaining eight are not significant. This is a non-significantly lower proportion of significant RRs than in the included studies (1/11 = 9% compared with 23/87 = 36%).

Table C5: Lifetime Asthma/Parent Exposure

Table C5 is similar to Table C1 except that the definition of exposure changes from "total" to "parent." Thus studies which have results available only for biochemically-assessed exposure, total questionnaire-assessed ETS exposure or overall household ETS exposure are excluded, while for studies which have both those exposures and parental exposure, the parental exposure is now selected for the meta-analysis. Overall, there are 72 RRs available, 56 of which are identical to those in Table C1. Among the studies for which a different RR is now selected, there is a change in the significance of the RR in only two (ANNESI, WITHER), where the parental RR is significantly greater than 1.00 while the total RR is not, and no consistent direction of change among the others. The overall RR adjusted for covariates is 1.27 (1.23-1.32) for the fixed effects analysis and 1.27 (1.21-1.33) for the random effects analysis (both $p<0.001$). RRs unadjusted for covariates are virtually identical. There is no significant evidence of publication bias. The fixed and random effects estimates are quite similar, because there is much less evidence of heterogeneity, the heterogeneity chisquared of 109.15 on 71 d.f. being significant only at $p<0.01$, the large LEE3 study with a low RR for total exposure not reporting any results for parental ETS exposure. Six factors show significance on a heterogeneity analysis.

- RRs vary by country in Asia, being lower in Far East studies (1.07, 0.89-1.29, n=5) than for Middle East studies (1.36, 1.18-1.57, n=6), there being only one Central/South East study with relevant data;
- RRs are lower where the child was the respondent for ETS exposure (1.02, 0.89-1.17, n=6) than where the parent was (1.28, 1.22-1.35, n=46), the information came from medical records (1.31, 1.24-1.38, n=3) or where it came from mixed or other sources (1.28, 1.18-1.39, n=17);
- RRs are similarly lower where the child was the respondent for diagnoses;
- RRs are slightly lower where the ISAAC questionnaire was used (1.17, 1.09-1.26, n=13) than where the ATS questionnaire was (1.29, 1.17-1.41, n=10) or where neither of these was used (1.30, 1.25-1.36, n=49);
- RRs vary by the exposure source, being highest for the mother (1.30, 1.26-1.35, n=44), intermediate for any parent (1.21, 1.12-1.31, n=23) and lowest for father (1.02, 0.85-1.23, n=5); and
- RRs also vary quite similarly for the unexposed group, this analysis being strongly correlated with the previous one.

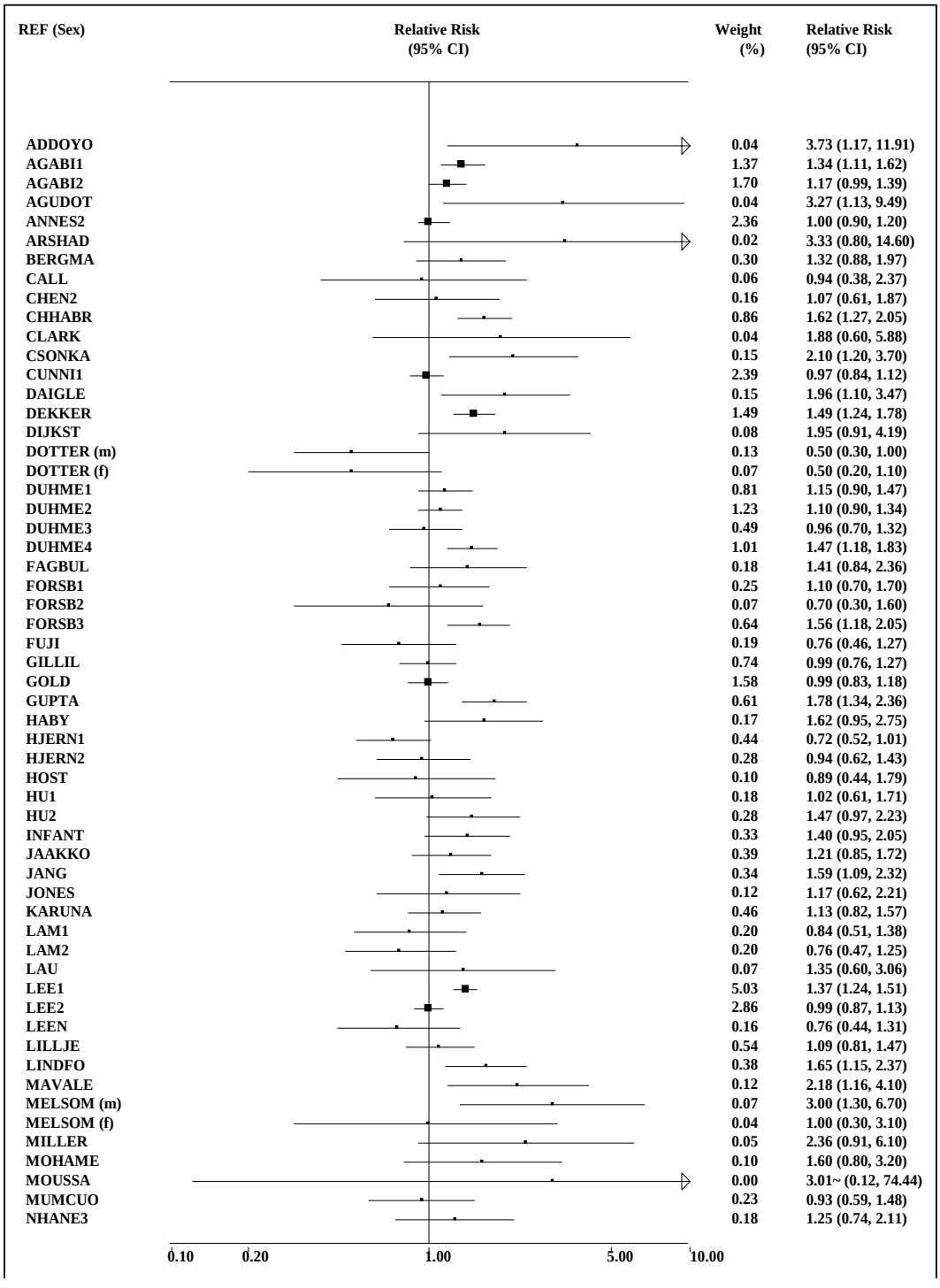

Figure 9.2. (Continued)

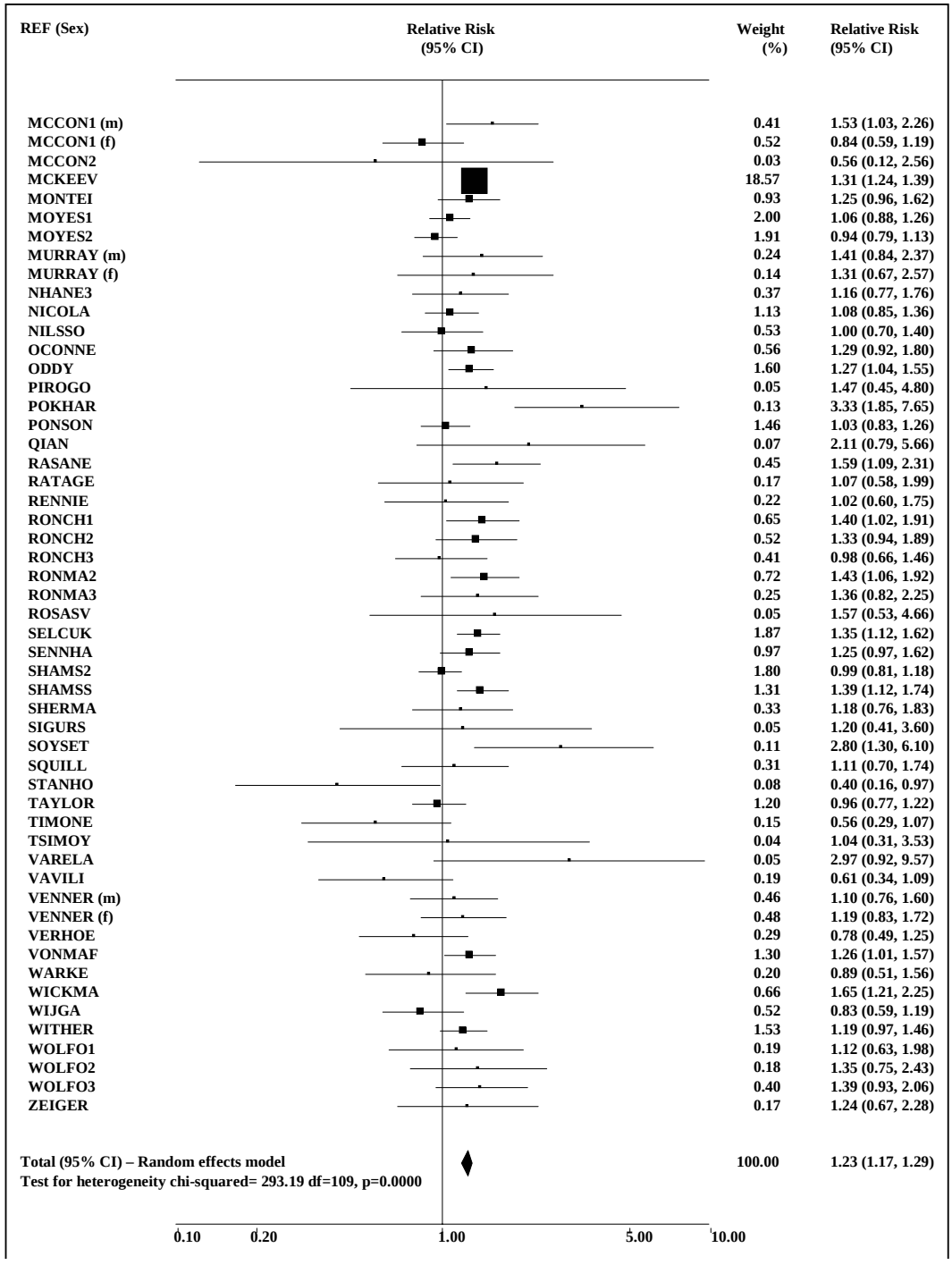

Figure 9.2. Forest plot for current asthma and total in-life exposure – children[1].

[1] Asthma outcome: current; source of ETS exposure: total (or nearest equivalent); time of ETS exposure: general; definition of non-exposure: most; these terms are defined in §7.10.5. Data as used in Table C3. The RRs used are adjusted for covariates where adjusted data are available.

~ Calculated using correction for zero cell (§7.9).

As discussed previously, results presented here by source of exposure are limited, as exposure by the mother or father is only chosen when exposures higher on the preference list are not available.

Five studies had alternative RRs which would have been selected as higher preference had they been completely reported. For two studies, the incomplete RR is non-significant (RASANE) or close to 1.00 (ALFRA1) whereas that included is significant. For the other three studies, the incomplete and the included risks are either both significant or both non-significant.

14 studies provide only incomplete RRs – four significant and 10 not significant.

Table C7: Current Asthma/Parent Exposure

This analysis varies from Table C1 in both definition of asthma and of exposure. Here there are 45 RRs available. Overall the increase in risk of current asthma in relation to parent exposure is highly significant ($p<0.001$), being estimated as 1.21 (1.14-1.28) for the fixed effects analysis and 1.21 (1.11-1.33) for the random effects analysis using RR estimates adjusted for covariates where possible, and somewhat higher, at 1.27 (1.20-1.34), for the fixed effects analysis and 1.26 (1.16-1.37) for the random effects analysis using RR estimates unadjusted for covariates where possible (Appendix Table C7). There is no significant evidence of publication bias. There is some evidence of heterogeneity ($p<0.001$) with the chisquared 80.44 on 44 d.f., but no specific study is a major contributor to this. Looking at specific factors one can observe:

- a lack of association in studies starting or publishing early;
- a stronger association in younger children;
- a lack of association if the child reported the asthma diagnosis;
- a lack of association where the ATS questionnaire was used;
- a stronger association in studies adjusting for family composition;
- a stronger association in studies adjusting for in-life ETS exposure; and
- a weaker association if exposure was “life/ever” than if it was current or unspecified (and similarly if non-exposure was “never” rather than “non”).

Many of these associations are similar to those noted in Table C3 for current asthma/total exposure.

Three studies had alternative RRs which would have been selected as higher preference had they been completely reported. For one of these (PALMIE) the incompletely reported RR was noted to be significant where the estimate used for the meta-analysis was not. For the other two studies, the incomplete and the included RRs are either both significant or both non-significant.

A further nine studies provide only incomplete data – one RR less than 1.00 with significance not stated, and the remainder all not significant.

Variants on Tables C1, C3, C5 and C7

Other Definitions of Exposure Time and of Non-exposure: Tables C1 to C24

Table 9.9 summarizes some relevant results (for covariate adjusted analyses) from Appendix Tables C1 to C24. These investigate how variations in the definitions of exposure time and of non-exposure affect the findings.

Table 9.9. Variant analyses by exposure time – children

Table[1,2]	Exposure time[1]	Non-exposure[1]	Number of estimates	Fixed effects RR (95% CI)[3]	Heterogeneity Chisq per df[4]
Outcome: lifetime; exposure: total (or nearest equivalent)					
C1[k]	General	Most	110	1.20 (1.17-1.23)	2.69***
C2	General	Least	110	1.20 (1.17-1.23)	2.69***
C9	Recent	Most	109	1.20 (1.17-1.23)	2.62***
C10	Recent	Least	110	1.20 (1.17-1.23)	2.66***
C17	Earliest	Most	109	1.20 (1.17-1.23)	2.64***
C18	Earliest	Least	109	1.20 (1.17-1.23)	2.64***
Outcome: lifetime; exposure: parent					
C5[k]	General	Most	72	1.27 (1.23-1.32)	1.54**
C6	General	Least	72	1.28 (1.24-1.32)	1.50**
C13	Recent	Most	72	1.27 (1.23-1.31)	1.49**
C14	Recent	Least	72	1.29 (1.24-1.33)	1.50**
C21	Earliest	Most	72	1.27 (1.23-1.31)	1.49**
C22	Earliest	Least	72	1.28 (1.24-1.32)	1.45**
Outcome: current; exposure: total (or nearest equivalent)					
C3[k]	General	Most	87	1.17 (1.15-1.20)	3.43***
C4	General	Least	87	1.17 (1.15-1.20)	3.43***
C11	Recent	Most	87	1.17 (1.15-1.20)	3.58***
C12	Recent	Least	87	1.17 (1.15-1.20)	3.61***
C19	Earliest	Most	87	1.17 (1.15-1.20)	3.43***
C20	Earliest	Least	87	1.17 (1.15-1.20)	3.43***
Outcome: current; exposure: parent					
C7[k]	General	Most	45	1.21 (1.14-1.28)	1.83***
C8	General	Least	45	1.21 (1.14-1.28)	1.83***
C15	Recent	Most	45	1.24 (1.17-1.31)	1.54*
C16	Recent	Least	45	1.23 (1.16-1.31)	1.60**
C23	Earliest	Most	45	1.21 (1.14-1.28)	1.83***
C24	Earliest	Least	45	1.21 (1.14-1.28)	1.83***

[1] Terms are defined in §7.10.5.

[2] Except for tables marked with a k (key), further results are only shown in the Appendix Tables.

[3] The RRs used are adjusted for covariates where adjusted data are available.

[4] Significance of heterogeneity: *** p<0.001, ** p<0.01, * p<0.05, (*) p<0.1, NS p≥0.1.

Table 9.10. Individual variant relative risks for recent exposure – children

Study	C7 general		C15 most recent	
	Exposure/ no exposure	RR (95% CI)	Exposure/ no exposure	RR (95% CI)
CHEN2	ever/never	1.11 (0.67-1.83)	current/non	1.02 (0.55-1.90)
GOLD	ever/never	0.99 (0.83-1.18)	current/non	1.10 (0.92-1.31)
HJERN1	ever/never	0.72 (0.52-1.01)	current/non	0.87 (0.58-1.30)
HJERN2	ever/never	0.94 (0.62-1.43)	current/non	0.81 (0.45-1.47)
TARIQ	in-life/non	0.89 (0.57-1.40)	current/non	1.20 (0.30-2.70)

Given the outcome, the exposure and the exposure time (i.e. by comparison of successive pairs of results), it can be seen that whether or not non-exposure is based on a preference for the "most" unexposed group (both in terms of the source and of the timing of exposure – see §7.10.5) or for the "least" unexposed group, makes little or no difference to the findings. This is unsurprising because for many studies there is actually no available choice of a different most and least unexposed RR.

Given the outcome, the exposure and the definition of non-exposure, it also makes not a great deal of difference whether one uses the "general" definition of exposure, or chooses the available RR which relates to the most recent or the earliest exposure in the child's life. The only noticeable difference is for recent vs general (or earliest) for current asthma and parental exposure. Here, of the 45 RRs in analyses C7 and C15, only five differ between the two analyses. These are as shown in Table 9.10.

The main contributor to the slightly higher estimate of 1.24 (1.17-1.31) in Table C15 compared to 1.21 (1.14-1.28) is the GOLD study, which has by far the largest weight.

Generally, however, the data do not provide any reliable indication that the exact definition of time of exposure makes any difference to the RR obtained.

Other Definitions of Asthma Outcome: Tables C25 to C40

Table 9.11 summarizes further variants of these analyses, involving alternative definitions of the asthma outcome, from Appendix Tables C25 to C40. Results of the earlier analyses are repeated for convenience.

In Tables C1 to C24 studies for which data are only available for current asthma are not included in analyses of lifetime asthma, and *vice versa*. Tables C25 to C28 are based on more studies by introducing a preferencing on asthma outcome. In "lifetime/current" analyses, data for lifetime asthma are chosen if available and for current asthma if not, whereas in "current/lifetime" analyses data for current asthma are preferred. As seen from the above table, given the studies with data for either current or lifetime asthma, it makes little difference which order of preference was used. The estimated RRs for lifetime/current and current/lifetime tend to be intermediate between that of the lifetime and current analyses, and closer to that for the lifetime analysis, both in the exposure: total and exposure: parent analyses.

For Tables C25 and C26, analyses of heterogeneity are shown. Table C25 is based on a total weight of 13260 with major contributors being WANG (3689), MCKEEV (1119), STURM (884) and LEE3 (514). There is a large excess of the heterogeneity chisquared, 553.37, over the degrees of freedom, 171. Three of the four studies with large weight

contribute materially to this, with Q_s values of 74.32 for STURM, 69.55 for LEE3 and 34.56 for WANG. STURM has a relatively high risk estimate, with LEE3 and WANG having relatively low estimates. The marked heterogeneity complicates interpretation of the variation by factor level, many of the nominally significant variations seen in Table C25 not indicating true sources of variation. The variations can be seen from Table C25 itself, but are not discussed further here.

Table 9.11. Variant analyses by outcome – children

Table[1,2]	Asthma outcome[1]	No. of estimates	Fixed effects RR (95% CI)[3]	Random effects RR (95% CI)[3]	Heterogeneity Chisq per df[4]
Exposure: total (or nearest equivalent)					
C1[k]	Lifetime	110	1.20 (1.17-1.23)	1.23 (1.17-1.29)	2.69***
C3[k]	Current	87	1.17 (1.15-1.20)	1.20 (1.13-1.27)	3.43***
C25[k]	Lifetime/current	179	1.19 (1.17-1.21)	1.23 (1.18-1.28)	3.11***
C27	Current/lifetime	178	1.19 (1.17-1.21)	1.23 (1.18-1.28)	3.12***
C29	Onset	17	1.27 (1.21-1.34)	1.23 (1.12-1.36)	1.57(*)
C31[k]	Lifetime-physician	64	1.18 (1.14-1.22)	1.21 (1.13-1.30)	3.35***
C33[k]	Current-physician	32	1.19 (1.09-1.30)	1.23 (1.08-1.39)	1.79**
C35	Lifetime, age <10	26	1.28 (1.22-1.35)	1.27 (1.17-1.39)	1.93**
C36	Lifetime, age including 10	72	1.20 (1.17-1.24)	1.23 (1.16-1.31)	2.92***
C37	Lifetime, age >10	15	1.10 (1.02-1.18)	1.15 (1.01-1.31)	2.33**
Exposure: parent					
C5[k]	Lifetime	72	1.27 (1.23-1.32)	1.27 (1.21-1.33)	1.54**
C7[k]	Current	45	1.21 (1.14-1.28)	1.21 (1.11-1.33)	1.83***
C26[k]	Lifetime/current	108	1.27 (1.23-1.30)	1.26 (1.21-1.32)	1.58***
C28	Current/lifetime	108	1.26 (1.22-1.30)	1.25 (1.20-1.31)	1.63***
C30	Onset	14	1.27 (1.21-1.34)	1.23 (1.10-1.37)	1.57(*)
C32	Lifetime-physician	38	1.29 (1.24-1.35)	1.28 (1.19-1.37)	1.55*
C34	Current-physician	18	1.22 (1.08-1.39)	1.28 (1.03-1.58)	2.27**
C38	Lifetime, age <10	18	1.32 (1.25-1.39)	1.33 (1.20-1.46)	1.81*
C39	Lifetime, age including 10	46	1.28 (1.23-1.33)	1.26 (1.19-1.33)	1.31(*)
C40	Lifetime, age >10	9	1.21 (1.08-1.35)	1.24 (1.02-1.50)	2.34*

[1] In all these analyses, the exposure time is "general" and the non-exposure is "most" unexposed. Terms are defined in §7.10.5.

[2] Except for tables marked with a k (key), further results are only shown in the Appendix Tables.

[3] The RRs used are adjusted for covariates where adjusted data are available.

[4] Significance of heterogeneity: *** $p<0.001$, ** $p<0.01$, * $p<0.05$, (*) $p<0.1$, NS $p\geq0.1$

For Table C26, the excess of heterogeneity, 168.96, over the degrees of freedom, 107, is much smaller and there are no "outlying" results (large Q_s) with very large weight. Here the most notable variations are in relation to:

- low RRs if the child reported the asthma diagnosis; and
- higher RRs if exposure is from the mother rather than the father (and also for the corresponding breakdown by non-exposure).

Tables C29 and C30 are based on prospective studies where analyses of onset of asthma were conducted and on case-control studies of first occurrence of asthma. Here the number of RR estimates included is much lower (17 for total exposure and 14 for parent exposure), but highly significant ($p<0.001$) increases are seen in both Tables, with no clear evidence of heterogeneity ($0.05<p<0.1$). Of the 17 estimates for total exposure, 15 are greater than 1.00, the highest being 1.98, with four significantly positive, the only estimates less than 1.00 being 0.99 and 0.84. The overall estimate is 1.27 (1.21-1.34). Note that the total weight of 1616 is dominated by the weight of 1119 for the MCKEEV study, which has an RR of 1.31 (1.24-1.39).

Tables C31 to C34 are restricted to studies based on physician-diagnosed asthma. Meta-analysis estimates are generally quite similar to those for the corresponding analysis with no restriction on physician diagnosis (e.g. Table C1 vs C31 or Table C7 vs C34). However, being based on less RR estimates, particularly for current asthma, the confidence limits are rather wider and are not clearly significant for Table C34 (exposure: parent, current asthma). Analyses of heterogeneity are presented in the Tables and are not discussed further here.

Tables C35 to C40 are based on lifetime asthma, with RRs selected by the age of the child. In all the analyses significant associations of exposure with outcome are seen with some evidence of heterogeneity (though not always significant), as shown in Table 9.11 above. For both total and parent exposure there is a tendency for RR estimates to be highest where the children studied are aged less than 10, intermediate where the age range spans 10, and lowest for age more than 10. This is true both for fixed effects and random effect estimates.

Other Definitions of Exposure Source: Tables C41 to C69

In these analyses, the exposure source, previously total or parent in all analyses, is varied. Results are presented for each combination of lifetime or current asthma and most or least non-exposure. There are thus four tables for each exposure source. The results for most non-exposure are summarized below in Table 9.12. Results for least non-exposure (even-numbered Appendix Tables) tended to be very similar and are not discussed further here.

Where both parents smoke, RR estimates for both lifetime and current asthma, tend to be larger and more consistently positive than for the more general parent exposure analysis. For lifetime asthma there are nine RR estimates, all greater than 1.00, in the range 1.10 to 2.90 with six significantly positive, and no statistically significant heterogeneity. Although the fixed effects estimate for current asthma (1.41, 1.24-1.61) is similar to that for lifetime asthma (1.40, 1.24-1.58), it is based on more variable estimates, of 1.29, 1.35, 1.40, 1.94, 2.48, 3.30 and 11.00, with the lower confidence limit of the highest two estimates, 1.70 for the 3.30 and 2.50 for the 11.00, exceeding the overall estimate. As a result, the random effects estimate is somewhat higher, at 1.69 (1.25-2.27) for current asthma than the 1.44 (1.22-1.70) for lifetime asthma. Although heterogeneity analyses by factor level are included in Table C43, they are of little value.

Table 9.12. Variant analyses by exposure source – children

Table[1,2]	Exposure source[1]	No. of estimates	Fixed effects RR (95% CI)[3]	Random effects RR (95% CI)[3]	Heterogeneity Chisq per df[4]
Outcome: Lifetime asthma					
C1[k]	Total (or nearest equivalent)	110	1.20 (1.17-1.23)	1.23 (1.17-1.29)	2.69***
C5[k]	Parent	72	1.27 (1.23-1.32)	1.27 (1.21-1.33)	1.54**
C41[k]	Both parents	9	1.40 (1.24-1.58)	1.44 (1.22-1.70)	1.62 N.S.
C45[k]	Mother/mother only	49	1.30 (1.25-1.35)	1.31 (1.24-1.40)	1.85***
C49	Mother only	4	1.24 (1.02-1.51)	1.16 (0.80-1.67)	2.93*
C53[k]	Father/father only	35	1.18 (1.13-1.22)	1.16 (1.09-1.25)	2.03***
C57	Father only	6	1.11 (0.96-1.29)	1.11 (0.96-1.29)	0.80 N.S.
C61	Household exposure other than parents	4	1.41 (1.14-1.73)	1.41 (1.14-1.73)	0.87 N.S.
C65[k]	Household exposure but not mother	10	1.14 (1.01-1.29)	1.14 (1.00-1.30)	1.10 N.S.
Outcome: Current asthma					
C3[k]	Total (or nearest equivalent)	87	1.17 (1.15-1.20)	1.20 (1.13-1.27)	3.43***
C7[k]	Parent	45	1.21 (1.14-1.28)	1.21 (1.11-1.33)	1.83***
C43[k]	Both parents	7	1.41 (1.24-1.61)	1.69 (1.25-2.27)	2.59*
C47[k]	Mother/mother only	29	1.21 (1.14-1.29)	1.25 (1.12-1.40)	2.25***
C51	Mother only	5	1.33 (1.14-1.56)	1.38 (1.03-1.85)	2.12(*)
C55[k]	Father/father only	24	1.04 (0.97-1.10)	1.02 (0.94-1.10)	1.24 N.S.
C59	Father only	6	1.14 (1.00-1.31)	1.15 (0.98-1.34)	1.10 N.S.
C63	Household exposure other than parents	6	1.49 (1.30-1.71)	1.49 (1.30-1.71)	0.89 N.S.
C67[k]	Household exposure but not mother	6	1.14 (1.00-1.31)	1.15 (0.98-1.34)	1.10 N.S.

[1] In all these analyses, the exposure time is "general" and the non-exposure is "most" unexposed. Terms are defined in §7.10.5.

[2] Except for tables marked with a k (key), further results are only shown in the Appendix Tables.

[3] The RRs used are adjusted for covariates where adjusted data are available.

[4] Significance of heterogeneity: *** p<0.001, ** p<0.01, * p<0.05, (*) p<0.1, NS p>0.1.

Tables C45 to C48 relate to whether the mother smokes. While the analysis is run using a preference for mother regardless of father, then mother only, in nearly all cases the RR selected was for mother regardless of father, the only exception being study GILLIL in Tables C47 and C48 where the RR was for mother only. These can be contrasted with the much sparser data for Tables C49 to C52 relating to whether, specifically, the mother only smokes. Similarly Tables C53 to C56 relate to whether the father smoked and Tables C57 to C60 to whether the father only smoked. Again the data for father smoked are mainly for father regardless of mother, the only exceptions being study VENNER in Tables C53 and C54 and studies GILLIL and SHIVA in Tables C55 and C56 where the RRs were for father only smoked.

With asthma outcome (lifetime or current), use of preference (e.g. mother/mother only or mother only specifically) and type of meta-analysis estimate (fixed effects or random effects) held constant, it is clear that estimates based on mother as the exposure source are always greater than the corresponding estimate based on father as the exposure source. While the eight mother-based estimates in Table 9.12, with one minor exception, are all statistically significant, only two of the eight father-based estimates are.

For father smoking, there is no real evidence at all of an increase in risk in the results for current asthma. Thus, in Table C55, one has 24 RR estimates, 11 greater than 1.00, 13 less than 1.0, and only one statistically significant (a marginally significant, p=0.049, increase in the AGABI2 study), and with no evidence of heterogeneity. Furthermore, there are an additional five studies with incomplete data, four of which reported no significant association of father smoking with current asthma, the other reporting a RR of 1.13 likely also to be non-significant.

In Table C53, for lifetime asthma, there is a significant increase in relation to father/father only exposure, with the fixed effects RR 1.18 (1.13-1.22, p<0.001). However, there is considerable heterogeneity in the data (χ^2_{het} = 69.17 on 34 d.f., p<0.001), with estimates varying from a significant decrease of 0.77 (0.60-0.98) for the LISTER study to a significant increase of 2.73 (1.92-3.88) for the ALDAWO study. Both these studies are major contributors to the heterogeneity, with the Q_s values 22.10 for ALDAWO and 11.47 for LISTER. Nevertheless the random effects RR estimate is still significant (1.16, 1.09-1.25, p<0.001), with 26 individual estimates greater than 1.00 and eight less than 1.00 (and one is equal to 1.00). However it should be noted that there are an additional four studies with incomplete data, three of which reported no significant association of father smoking with lifetime asthma, the other reporting RRs of 0.84 and 0.65 for boys and girls respectively, also consistent with no association.

For mother smoking, the data seem far more consistently positive. For mother/mother only and lifetime asthma (Table C45), 42 of the 49 RR estimates are greater than 1.00, 23 significantly so (at p<0.05), with only seven less than 1.00, one significant, and no very obvious outliers. Though there is statistically significant heterogeneity (χ^2_{het} = 88.85 on 48 d.f.; p<0.001), no single factor shows marked (p<0.01) heterogeneity. Of eight studies with incomplete data which reported statistical significance, four (50.0%) reported a significant positive association, in line with the 48.9% (23/47) in the studies considered in Table C45.

For mother/mother only and current asthma (Table C47), the data are rather more heterogeneous, with eight of the 29 estimates greater than 2.00 and seven less than 1.00 (χ^2_{het} = 63.01 on 28 d.f., p<0.001), but the tendency to a positive association seems clear enough. However, this tendency seems less evident in the six studies with incomplete data, none of which reported a significant association.

The analyses described above show a stronger association of maternal than paternal smoking with current or lifetime asthma. To gain further insight into this, two further investigations were conducted.

Table 9.13. Individual relative risks by source of parental exposure – children

Outcome	Study	Adjustment variables	RR (95% CI)[1]		
			Mother only	Father only	Both parents
Lifetime asthma	DOLD	0	1.36 (1.02-1.82)	1.14 (0.84-1.55)	1.11 (0.82-1.51)
	FERGUS	0	0.62 (0.33-1.15)	1.28 (0.85-1.94)	1.10 (0.75-1.63)
	FORAST	9	1.70 (1.04-2.70)	1.00 (0.70-1.50)	1.50 (1.04-2.20)
	KAY	1	1.18 (0.73-1.91)	1.29 (0.83-2.01)	1.93 (1.23-3.01)
Current asthma	AGABI1	11	1.46 (1.13-1.87)	1.26 (1.01-1.58)	1.35 (1.09-1.69)
	AGABI2	12	1.23 (0.98-1.53)	1.04 (0.86-1.27)	1.29 (1.06-1.56)
	GILLIL	8	0.90 (0.50-1.50)	1.10 (0.70-1.80)	1.40 (0.90-2.30)
	MAVALE	0	6.19 (0.71-54.36)	1.93 (0.98-3.80)	2.48 (0.44-13.96)
	WILLE1	0	3.27 (1.22-8.75)	0.94 (0.30-2.97)	1.94 (0.74-5.12)

[1] The RRs are adjusted for covariates where adjusted data are available. They are all for sexes combined and are relative to the unexposed group "neither parent smoked" (or in study GILLIL "no household member smoked").

First, as shown in Table 9.13, RRs were compared within study for mother only smoked, father only smoked and both parents smoked for those nine studies providing directly comparable data. The denominator for all the RRs was "neither parent smoked" or, in the case of one study, "no household member smoked." (This is not the same as the data used for mother only in Tables C49 and C51 or for father only in Tables C57 and C59, where the preference was to use "not the specific parent" as the denominator.)

Making inferences about the relative associations of maternal and paternal smoking from these data is difficult due to the wide confidence limits in some studies (particularly MAVALE and WILLE1), and also to the fact that for three of the studies (FERGUS, GILLIL, MAVALE) no significant association was seen for any of the three RRs. However, the results are generally consistent with the association being more with maternal than paternal smoking. Thus, in the nine studies, the highest RRs were seen for mother only smoking in five, for both parents smoking in three and for father only smoking in only one. Similarly, where significant increases were seen these were seen for mother only smoking in four studies, for both parents in four studies and for father only smoking in only one. In that study, AGABI1, the significance for father only smoking was only marginal (lower CI = 1.01) and the RR estimate for father only smoking was lower than the other two estimates.

Second, the effect on maternal smoking RR estimates of adjusting for paternal (or non-maternal) smoking was investigated, as was the effect on paternal smoking RR estimates of adjusting for maternal smoking. Apart from the studies already considered in Table 9.13, comparison was between an unadjusted result and a result adjusted for a number of factors of which the maternal (or paternal) smoking was only one. Moreover many studies gave incomplete information for the adjusted result, and no meaningful conclusions could be drawn.

Tables C61 to C64 relate to household exposure other than the parents. For lifetime asthma there are only four estimates, giving an overall estimate of 1.41 (1.14-1.73) which is significant ($p<0.01$) and with no heterogeneity. All three relate to other household exposure irrespective of smoking by the parents (ALDAWO and MONTEI – any other household member, LAM2 – grandparents, RATAGE – grandfather). Only for study RATAGE is the

estimate significantly above 1.00. For study LAM2, an estimate of 0.71 (0.28-1.78) for siblings smoking is also available.

For current asthma there are six estimates, which give an overall estimate of 1.49 (1.30-1.71) which is significant at $p<0.001$, without heterogeneity. Only one of these estimates is for other household only exposure (i.e. without exposure from parents) and that shows no association – GILLIL, 1.00 (0.60-1.90). For study LAM2 an estimate of 0.49 (0.07-3.36) for siblings smoking is also available. Three studies also report incomplete results, two non-significant and one a RR of 1.13 which is probably also non-significant.

Tables C65 to C68 relate to household exposure other than from the mother, and are specifically restricted to where there is no exposure from the mother. For current asthma, the only available results are for father only, so that Tables C67 to C68 are identical to Tables C59 to C60. However for lifetime asthma, four studies provide estimates for household member other than mother, in addition to the six already considered for father only in Tables C57 to C58. The 10 estimates give an overall estimate of 1.14 (1.01-1.29) which is marginally significant at $p<0.05$, without heterogeneity.

Discontinued Exposure: Tables C69 and C70

Table C69 (lifetime asthma) and Table C70 (current asthma) both relate to household or parental ETS exposure, but specifically concern exposure that has been discontinued. This includes having a parent who is an ex-smoker, but not specific *in utero* exposure.

Table C69 is based on seven RR estimates, which together give a fixed effects estimate of 1.20 (1.11-1.30). As there is no evidence of heterogeneity, with the chisquared per degree of freedom less than 1 (0.60), the random effects estimate is the same. The significant finding leans heavily upon the estimate of 1.22 (1.12-1.33) from the MCKEEV study which has a weight of 513, 85% of the total weight. Of the other six estimates, four are greater than 1.00, two less than 1.00, and none statistically significant.

For current asthma, Table C70 is based on eight RR estimates, one significantly greater than 1.00, which together give a fixed effects estimate of 1.02 (0.94-1.12). There is some heterogeneity (χ^2_{het} = 12.76 on 7 d.f., $p<0.1$), but the random effects estimate is similar, at 1.01 (0.88-1.15).

9.3.3. Risk by Amount of Exposure in Life – Table D and Appendix Table D

All analyses considered in §9.3.3, and presented in Table D (and in Appendix Table D in more detail), have the restriction, in addition to those already defined in §7.10.4, that the RRs are selected for exposure in the child's lifetime if available, otherwise for alternatives as already defined in §9.3.2, and that the exposure is subdivided into categories by amount of exposure, with each category compared with a base group of no exposure if available, otherwise of "no + low" exposure. Number of cigarettes is the most common measure of exposure, followed by number of persons in the household who smoke. Two studies (CHEN2 and CUNNI1) used both these measures, while ZHENG used persons and minutes per day, and STURM used persons and days/month. MAIER categorized exposure as *"none," "occasionally"* or *"several hours/day,"* and DUHME1 and DUHME3 as *"never," "seldom"* or *"constant."* Three studies (EHRLI2, NHANE3, WILLE1) used cotinine as the measure.

Table D and Appendix Table D both present results for six meta-analyses (Table 9.14).

In all these tables, the source of exposure is "total," the time of exposure is "general," and the unexposed group is "most," as explained in §7.10.5. Additional tables where the unexposed group is "least" are discussed later in this section but are not presented. Five studies presented results both for exposure from the mother and the father, and the RRs included in Table D are based on exposure from the mother. Additional analyses choosing exposure from the father rather than from the mother for these studies were also run and are discussed later in this section, but are not presented.

Only the factors *sex* and *measure of exposure* are considered in these Tables.

Lifetime Asthma: Tables D1-D2

There are a total of 19 pairs of RRs included in the adjusted meta-analyses. For all but four pairs, as is evident in Figure 9.3, the high dose RR is greater than the low dose RR. In the low dose analysis (Table D1) two RRs are significantly less than 1.00 and one significantly greater than 1.00, compared with none significantly less than 1.00 and six significantly greater than 1.00 in the high dose analysis (Table D2). Overall, there is no increased risk of lifetime asthma for low dose exposure, with a RR of 0.95 (0.89-1.02), but a significant increase for high dose exposure, with a RR of 1.22 (1.10-1.36) for the fixed effects model. Estimates are higher with the random effects model but the low dose estimate remains non-significant (low dose: 1.07 (0.93-1.22); high dose: 1.39 (1.16-1.68)). Results are also similar when unadjusted RRs are chosen in preference, and in the following text, attention is restricted to the adjusted analyses. The high dose analysis shows significant evidence of publication bias ($p<0.01$). There is evidence of heterogeneity in both analyses (low dose: $\chi^2_{het} = 44.14$ on 18 d.f., $p<0.001$; high dose: $\chi^2_{het} = 43.72$ on 18 d.f., $p<0.001$) Low estimates in the LEE3 study (low dose: 0.81 (0.73-0.89); high dose: 0.83 (0.68-1.00)) are major contributors to the heterogeneity in both analyses (low dose $Q_s = 10.56$, high dose $Q_s = 15.48$). A high estimate of 2.26 (1.37-3.73) in the MAIER study at the low dose also contributes ($Q_s = 11.46$). RRs did not vary materially according to the dose measure used (cigs/day, persons or other).

Table 9.14. Dose-response analyses for in-life exposure – children

Table	Asthma outcome	Amount of exposure
D1	Lifetime	Low
D2	Lifetime	High
D3	Current	Low
D4	Current	High
D5	Lifetime/current	Low
D6	Lifetime/current	High

Terms are defined in §7.10.5 and §7.10.7

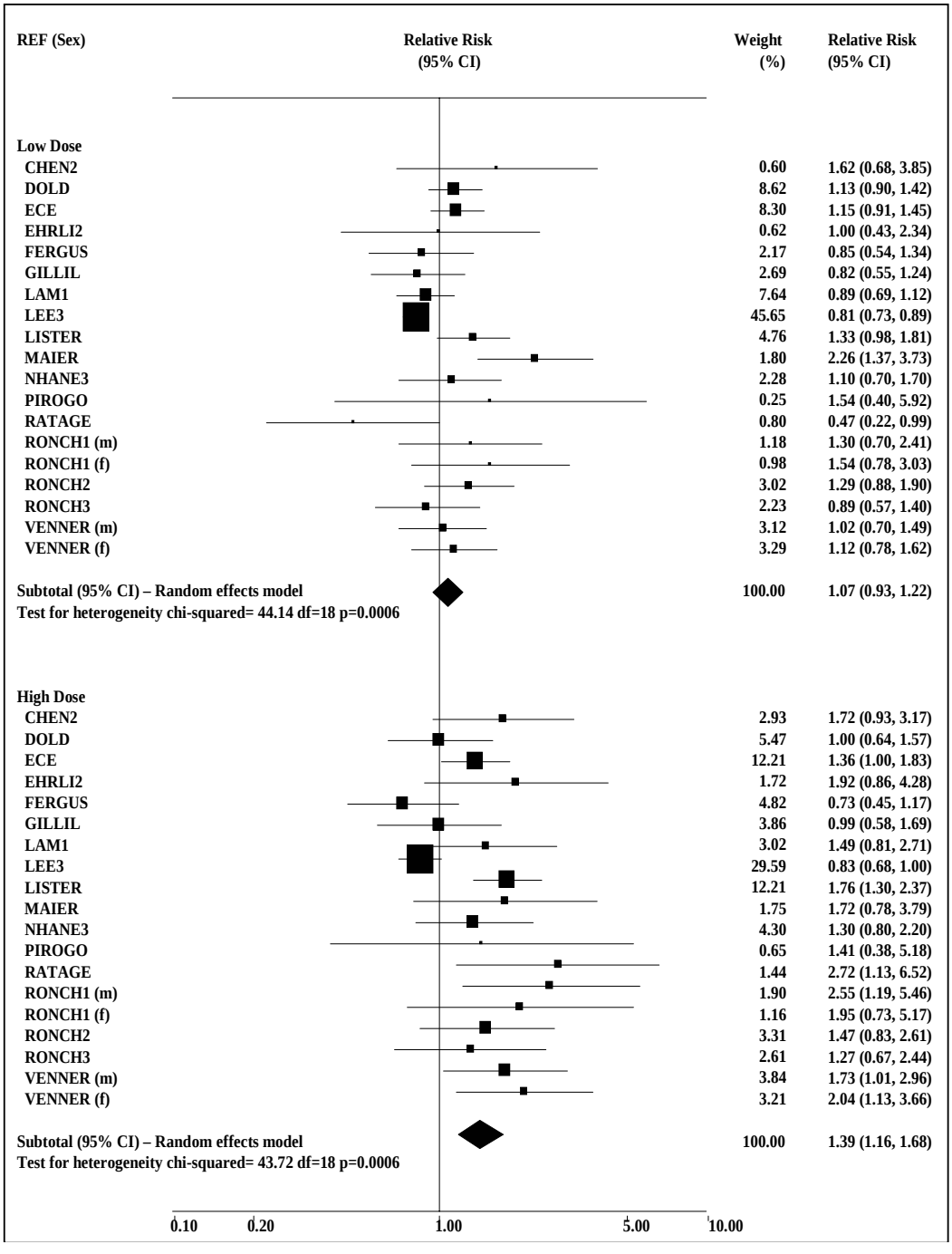

Figure 9.3. Forest plot for lifetime asthma and total in-life exposure by amount – children[1].

[1] Asthma outcome: lifetime; source of ETS exposure: total (or nearest equivalent); measure of dose: cigarettes or hours per day, smokers in household, or cotinine; these terms are defined in §7.10.5. Data as used in Tables D1 and D2. The RRs used are adjusted for covariates where adjusted data are available.

As described in §9.2 and Table 9.6, four studies provide dose-response data in forms that cannot readily be included into the analyses in Tables D1 and D2. For biochemically assessed exposure, EHRLI2 reports a significant increase in risk of 1.009 per ng/ml of urinary cotinine, but a non-significant increase of 1.004 for CCR. PONSON reports a non-significant increase of 1.04 per 20 cigarettes smoked in the household at time of birth. KASPER reports a significant (p=0.01) correlation between the probability of asthma and the number of cigarettes smoked at home, recorded as 0, 1-10, 11-20 … 71-80. ALFRA1 reports a significant association with number of cigarettes smoked by both parents but without any further detail[18]. A further three studies[19] provide only incomplete categorical data. In all three, both the low and high dose RRs were less than 1.0 with significance not stated, and the high dose RR was lower than the low dose RR.

Current Asthma: Tables D3-D4

Whereas Tables D1-D2 consider meta-analysis of lifetime asthma, Tables D3-D4 consider results for current asthma, other preferences being identical.

The 21 pairs of RRs, all for sexes combined[20], are shown in Figure 9.4. The high dose RR is greater than the low dose RR in 17 studies, equal in one and lower in three. In the low dose analysis (Table D3), there are four RRs significantly greater than 1.00, and two significantly less than 1.00, while in the high dose analysis (Table D4) there are ten RRs significantly greater than 1.00 and none significantly less. Using the fixed effects model there is a significant increased risk of current asthma in relation to both low dose exposure (1.20, 1.14-1.27), and to high dose exposure (1.53, 1.45-1.62). With the random effects model the overall estimates are reduced, to a non-significant 1.08 (0.97-1.21) for low dose, and to 1.40 (1.22-1.60) for high dose. In both the high and low dose analyses, there is significant heterogeneity (low dose: χ^2_{het} = 47.18 on 20 d.f., p<0.001; high dose χ^2_{het} = 60.95 on 20 d.f., p<0.001). No specific studies are major contributors to the high dose heterogeneity, but for the low dose low RRs in the LAM1 study (0.48, 0.25-0.93) and MUMCUO study (0.51, 0.31-0.86) had high Q_s values (LAM1 7.48, MUMCUO 10.30) which help to explain the higher overall RR estimate for the random effects analysis. There is some evidence in the high dose analysis that estimates from studies categorizing by numbers of cigarettes smoked by parents/household members are higher than for studies using other measures of dose. However, given the widely differing definitions of "high dose" within each type of measure, this finding probably has little real meaning. There is some evidence of publication bias (p<0.01) in the low dose analysis but not in the high dose analysis.

[18] There were some concerns about the quality of statistical analysis in this study, see §9.1.3, §9.2 and Table 9.7.

[19] Including the partially overlapping studies WOLFO1 and WOLFO2, see §9.1.3.

[20] Study KABESC had a high dose but not a low dose RR and is not included.

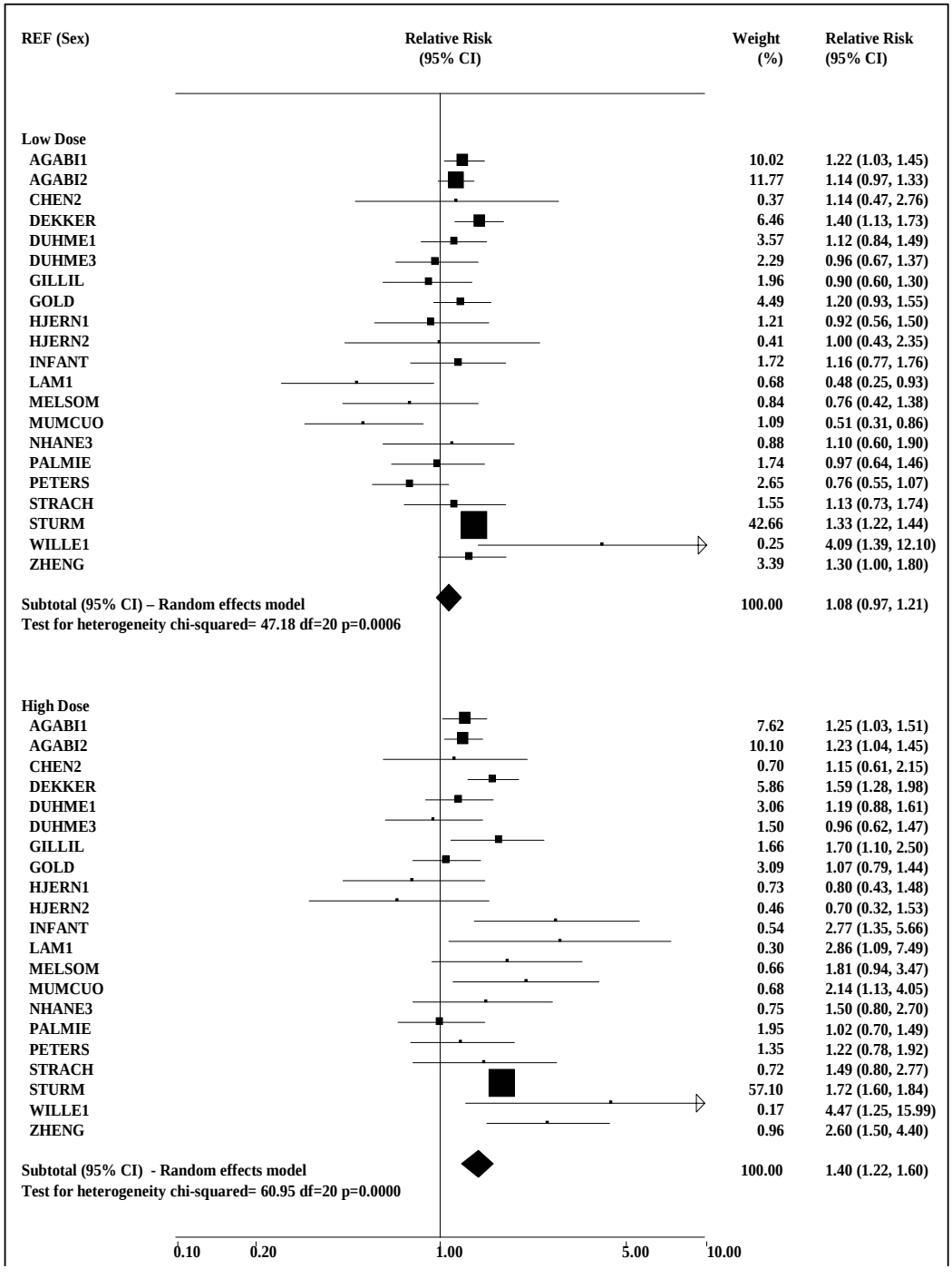

Figure 9.4. Forest plot for current asthma and total in-life exposure by amount – children[1].

[1] Asthma outcome: current; source of ETS exposure: total (or nearest equivalent); measure of dose: cigarettes per day, days per month, seldom/constant, smokers in household, or cotinine; these terms are defined in §7.10.5. Data as used in Tables D3 and D4. The RRs used are adjusted for covariates where adjusted data are available.

As described in §9.2 and Table 9.6, seven studies provide dose-response data that cannot readily be included into the analyses in Tables D3 and D4. Four (CHINN, EHRLI1, TARIQ and SCHMIDT) report a non-significant association, and one (DIJKST) a negative association but with significance not stated (RR per 10 cigarettes 0.93). SOMERV reports a marginally significant positive association for boys but not for girls. KNIGHT studied four measures of exposure and reports a significant positive association for hair cotinine, but a non-significant negative association for the other three measures (number of cigarettes smoked by household members, urinary cotinine and urinary CCR).

A further four studies provide only incomplete categorical results. One (STRACH) merely gives results as non-significant for both low and high dose, while the other three studies give RRs without CIs or significance: for CUNNI1 both RRs are greater than 1.00, with the low dose RR greater than the high dose RR; for LAM2 both RRs are less than 1.00, with the low dose RR less than the high dose RR; and for WOLFO2 the low dose RR is less than 1.00 and the high dose RR is greater than 1.00.

Variants on Tables D1-D4

Lifetime/current Asthma: Tables D5-D6

The meta-analyses discussed above chose either lifetime asthma only, or current asthma only. In Tables D5-D6 more studies are included by introducing a preferencing on asthma outcome, with data for lifetime asthma chosen if available or for current asthma if not, giving 36 pairs of RRs. As in Tables D1-D4, there is clear evidence of an increase at high dose (1.46, 1.39-1.53) with the increase less marked at low dose (1.10, 1.06-1.15). The increase at low dose becomes non-significant using the random effects model (1.09, 0.99-1.19).

Other Definitions of Source of Exposure/non-exposure

Additional analyses (not presented) vary the preferencing by choosing the “least” unexposed comparison group rather than the “most” as in Tables D1-D4. For lifetime asthma, there is no change in the RRs selected for the analysis, while for current asthma there are some changes (RRs with exposure: “current” and non-exposure: “non” replaced by exposure: “current” and non-exposure: “never”) but this has virtually no effect on the overall estimates or the heterogeneity.

Further analyses also vary the preference by choosing paternal rather than maternal exposure if available. For lifetime asthma, only one alternative pair of RRs is selected, giving little change to the results. For current asthma, alternative RRs are selected from four studies. Here the overall estimates are somewhat lower than when maternal exposure is preferred – low dose: 1.15 (1.09-1.21), high dose: 1.53 (1.45-1.62). Heterogeneity is also somewhat higher than in the analysis with maternal exposure, and the random effects estimates (low dose: 1.01 (0.89-1.15), high dose 1.32 (1.13-1.54)) differ somewhat from the fixed effects estimates given in §4.3, particularly for low dose.

9.3.4. Risk from *In Utero* Exposure (Irrespective of In-life Exposure) – Table E and Appendix Table E

All analyses considered in §9.3.4 and presented in Table E (also presented in Appendix Table E in more detail) have the restriction, in addition to those already defined in §7.10.4, that the RRs are selected for exposure during gestation (*in utero* exposure of the fetus to maternal smoking). Table E presents results for three meta-analyses, Tables E1 and E2 relating to exposure from the mother being a smoker, with Table E3 relating to exposure from the father being a smoker or the mother being ETS exposed. Tables E1 and E3 relate to lifetime asthma, or current asthma if lifetime asthma is not available, while Table E2 relates to current asthma, or lifetime asthma if current asthma is not available. Only Table E1 includes detailed heterogeneity analyses.

Maternal Smoking in Pregnancy: Tables E1 and E2

31 studies provide estimates of risk in relation to maternal smoking. In all but one study the RRs relate to mother smoked vs mother did not smoke. In the CUNNI1 study, the RR relates to mother smoked vs no household member smoked. Relevant meta-analysis results are summarized in Table 9.15.

Table 9.15. Summary of *in utero* analyses – children

Table	Asthma outcome[1]	Adjusted for covariates	Fixed effects RR (95% CI)[2]	Random effects RR (95% CI)[2]	Heterogeneity Chisq per df[3]
E1[4]	Lifetime/current	Adjusted	1.28 (1.21-1.35)	1.31 (1.19-1.45)	2.27***
	Lifetime/current	Unadjusted	1.35 (1.29-1.42)	1.38 (1.26-1.52)	2.56***
E2[5]	Current/lifetime	Adjusted	1.28 (1.21-1.36)	1.33 (1.20-1.46)	2.24***

[1] Terms are defined in §7.10.5.
[2] The RRs used are adjusted for covariates where adjusted data are available, except in the unadjusted analysis where unadjusted data are used if available.
[3] Significance of heterogeneity: *** $p<0.001$, ** $p<0.01$, * $p<0.05$, (*) $p<0.1$, NS $p\geq0.1$.
[4] Analyses based on 32 RR estimates.
[5] Analyses based on 31 RR estimates.

All the analyses show a highly significant ($p<0.001$) elevated risk of childhood asthma associated with maternal smoking in pregnancy.

The analyses using the lifetime/current preference are based on 19 estimates using lifetime asthma and 13 using current asthma. Those based using the current/lifetime preference are based on 15 estimates using lifetime asthma and 16 using current asthma. This is because only three studies (GILLIL, HU1, WEITZ1) had RRs available for both outcomes, and study GILLIL had sex-specific results for lifetime asthma but only sexes-combined results for current asthma. One gave a higher RR estimate using lifetime/current, and two gave a lower RR. The overall results are so similar that the results for Table E2 will not be considered further.

The analyses using data adjusted for covariates where available include 23 adjusted and nine unadjusted estimates. Those using the data unadjusted for covariates where available include six adjusted and 26 unadjusted estimates. Here 17 studies have both adjusted and

unadjusted estimates. We will consider first the results using adjusted estimates where available.

For the adjusted analysis shown in Figure 9.5, 27 of the 32 RR estimates are greater than 1.00, with 12 statistically significant at $p<0.05$. None of the five RRs less than 1.00 are statistically significant. The fixed effects RR estimate is 1.28 (1.21-1.35), with significant evidence of heterogeneity ($\chi^2_{het} = 70.34$ on 31 d.f., $p<0.001$) and a random effects estimate of 1.31 (1.19-1.45). No single study is responsible for the heterogeneity, the largest Q_s being 7.98 for study KUEHR with an estimate of 0.61 (0.37-1.03). Of the total weight of 1284, one study (JAAKK2) has a weight of 277, with five other studies each having a weight of about 100 (varying between 89 and 114).

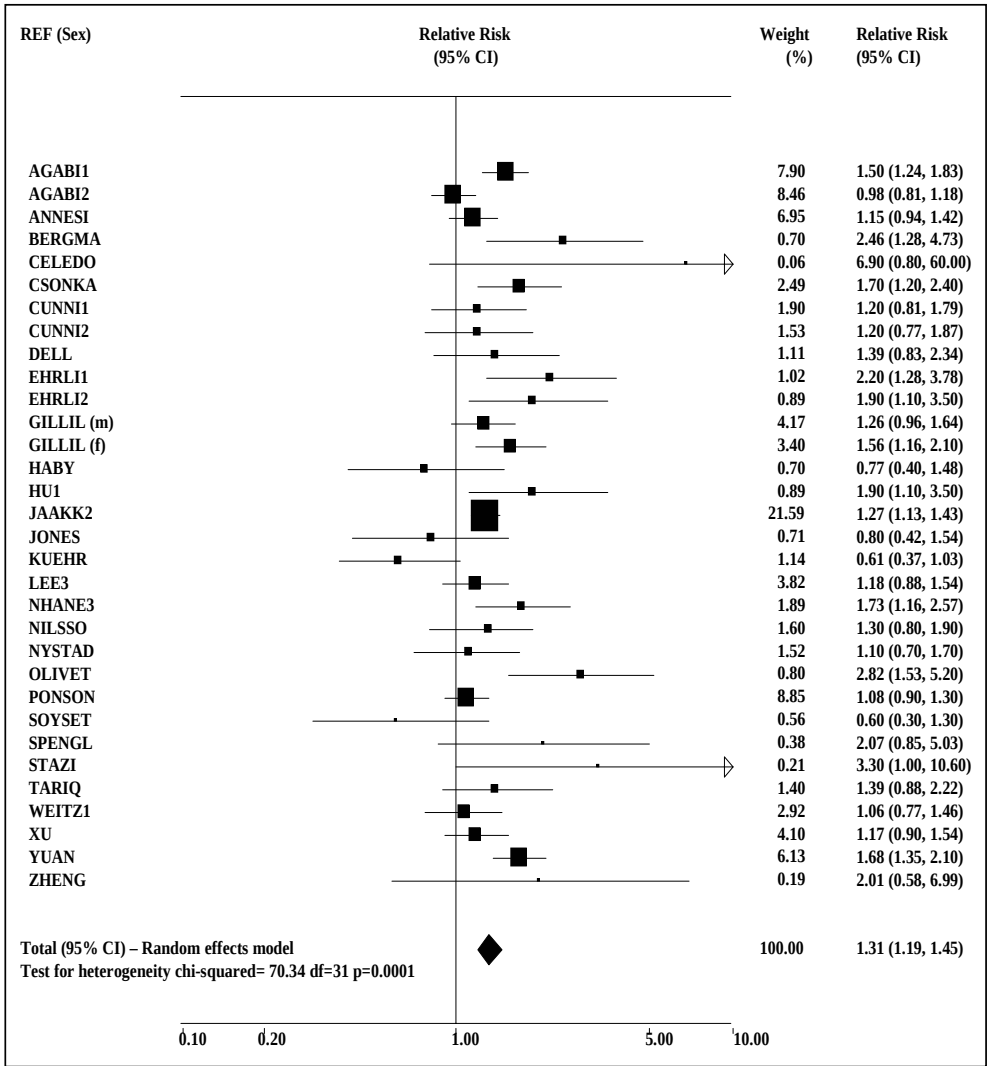

Figure 9.5. Forest plot for lifetime/current asthma and *in utero* exposure – children[1].

[1] Asthma outcome: lifetime/current; source of ETS exposure: maternal smoking in pregnancy; definition of non-exposure: most; these terms are defined in §7.10.5. Data as used in Table E1. The RRs used are adjusted for covariates where adjusted data are available.

Looking at how the RR estimates vary by factor level, the following main findings can be noted:

- *Sex.* 31 of the 32 studies report results only for the sexes combined so one cannot usefully see how estimates vary by the sex of the child;
- *Continent.* All but six of the studies were conducted in Europe or the USA. In the nine US studies estimates are somewhat higher (1.41, 1.24-1.59) than in the 16 European studies (1.27, 1.18-1.35). There is no significant variation by country within Europe;
- *Study type.* Of the 32 studies, 18 are cross-sectional, eight case-control and six prospective. Estimates do not vary markedly by study type;
- *Age of child.* Estimates do not vary significantly by the age of the child;
- *Population setting.* Estimates are larger in studies conducted in a medical setting (1.83, 1.34-2.50, n=4) than in studies conducted in a general setting (1.29, 1.20-1.40, n=11) or in a school setting (1.27, 1.16-1.38, n=16);
- *Respondent for smoking.* Estimates where the parent had supplied the data on smoking (1.20, 1.12-1.29, n=23) are lower than where the data came from other sources (χ^2_{het} = 9.03 on 3 d.f., p<0.01). In only one study, CELEDO, did the child report on this and here the RR was very high, 6.90, but with wide confidence limits, 0.80-60.0;
- *Child smokes.* Estimates where children who smoked were not included (1.47, 1.30-1.66, n=6) are higher than if they were included (1.04, 0.87-1.25, n=2) or if the question was ignored (1.26, 1.18-1.34, n=24);
- *Physician diagnosis.* Estimates are higher where the asthma had been diagnosed by a physician (1.35, 1.25-1.46, n=16) than where it may not have been (1.20, 1.11-1.30, n=16) (χ^2_{het} = 4.63 on 1 d.f., p<0.05);
- *Size of study.* Estimates do not vary significantly by the number of asthma cases studied;
- *Adjustment factors.* Estimates are higher in studies that adjusted for race (1.43, 1.26-1.64, n=9) than in studies that did not (1.25, 1.17-1.32, n=23), reflecting the fact that US studies are much more likely than other studies to adjust for race. Otherwise there is no evidence that estimates varied significantly according to which factors studies had adjusted for. There was little clear evidence of variation according to which factors the RRs themselves had been adjusted for; and
- *Asthma definition.* Estimates do not vary significantly by whether they were for lifetime asthma (1.26, 1.18-1.34, n=19) or current asthma (1.33, 1.20-1.48, n=13).

These conclusions are generally evident whether one considers the fixed effects analyses (cited above) or random effects analyses. It is clear that no factor, on its own, explains a major part of the overall heterogeneity.

As can be seen in the previous table, meta-analysis estimates based on unadjusted RRs tend to be higher than those based on adjusted RRs. Comparing the individual estimates, one sees that there are three studies in which the two estimates are substantially (>0.2) different (Table 9.16 and sections –2 and –5 of Appendix Table E1).

All of these show a larger unadjusted estimate. Of the other estimates which vary between the adjusted and unadjusted analyses, 11 show slightly larger unadjusted RRs and only four slightly larger adjusted RRs.

It should be noted that the unadjusted estimates have a very large heterogeneity (χ^2_{het} = 79.25 on 31 d.f., p<0.001). This is particularly due to a high Q_s value for NHANE3 (1.91, 1.56-2.33, Q_s = 11.27). However, despite the heterogeneity, the random effects estimate (1.38, 1.26-1.52) is only slightly larger than the fixed effects estimate (1.35, 1.29-1.42).

A further eight studies provide only incomplete results. Two studies (DEBENE, STERN2) report significant increases (STERN2 only for lifetime asthma), but the other six studies do not.

Table 9.16. Selected individual adjusted and unadjusted relative risks for *in utero* exposure – children

Study	Adjusted RR (95% CI)	Unadjusted RR (95% CI)
DELL	1.39 (0.83-2.34)	1.96 (1.21-3.17)
HABY	0.77 (0.40-1.48)	1.19 (0.81-1.74)
SOYSET	0.60 (0.30-1.30)	1.26 (0.71-2.25)

Other Exposure During Gestation: Table E3

Table E3 includes results from four studies, AGABI1 and AGABI2 for paternal smoking during the mother's pregnancy (with no adjustment for maternal smoking in pregnancy), MILLER (who excluded any mothers who smoked during pregnancy) for an exposure described as *"ETS exposure at home or at work during the entire course of the pregnancy"* and ZHENG (a study conducted in China which included few smoking mothers) for maternal ETS exposure during pregnancy. Three studies give estimates greater than 1.00, two significant, and one (the MILLER study) which had a small weight of only 4 of the total of 385 gave an estimate less than 1.00.

While the overall meta-analysis shows a significant RR of 1.18 (1.06-1.30), with no evidence of heterogeneity, 81% of the total weight comes from the AGABI1 and AGABI2 studies, which did not remove potential confounding by any effect of maternal smoking in pregnancy.

One further study (LOPEZC) reported a non-significantly increased RR for smoking by household members other than the mother which could not be included as no confidence interval was provided.

9.3.5. Risk by Amount of Exposure *In Utero* – Table F and Appendix F

The analyses considered in §9.3.5 and presented in Table F (also Appendix Table F in more detail) have the restriction, in addition to those already defined in §7.10.4, that the RRs are selected for exposure during gestation and that the exposure is subdivided into categories by amount of exposure as already defined in §9.3.3.

One pair of tables is presented, Table F1 for low exposure and Table F2 for high exposure, where "low" and "high" are as already described in §9.3.3. For both tables, the

outcome is "current/lifetime" and the source of exposure is "total," as explained in §7.10.5. Study WEITZ1 did have data for lifetime asthma but only for an age subset, so their data for current asthma were preferred. Otherwise, the alternative preferences described in §7.10.5 would not have made any difference to the RRs included in the Tables.

Tables F1 and F2 include results by amount of exposure *in utero* from five studies. In four of these, the measure of exposure is number of cigarettes smoked per day by the mother but in study ZHENG the results are for number of persons smoking in the presence of the mother during pregnancy.

Two other studies are not included in the meta-analyses. Study TAYLOR reported RRs of 1.29 for low exposure and 1.71 for high exposure (maternal cigarettes per day), but without information on significance. Study XU compared high and low exposure (maternal cigarettes per day) but omitting unexposed subjects.

There are five pairs of RRs included in the meta-analyses and shown in Figure 9.6. Results based on adjusted and unadjusted RRs are very similar, and attention is restricted here to the adjusted meta-analyses. For each study, the low dose RR is lower than the high dose RR. For the low dose, the RRs are generally close to 1.0 (JAAKK2 1.19, OLIVET 0.96, WEITZ1 1.20, YUAN 1.45, ZHENG 1.10) while the high dose RRs are usually greater than 2.0 (JAAKK2 1.29, OLIVET 11.32, WEITZ1 2.10, YUAN 2.10, ZHENG 3.30). All the high dose RRs are statistically significant ($p<0.05$) but for the low dose, only those in the JAAKK2 and YUAN studies are.

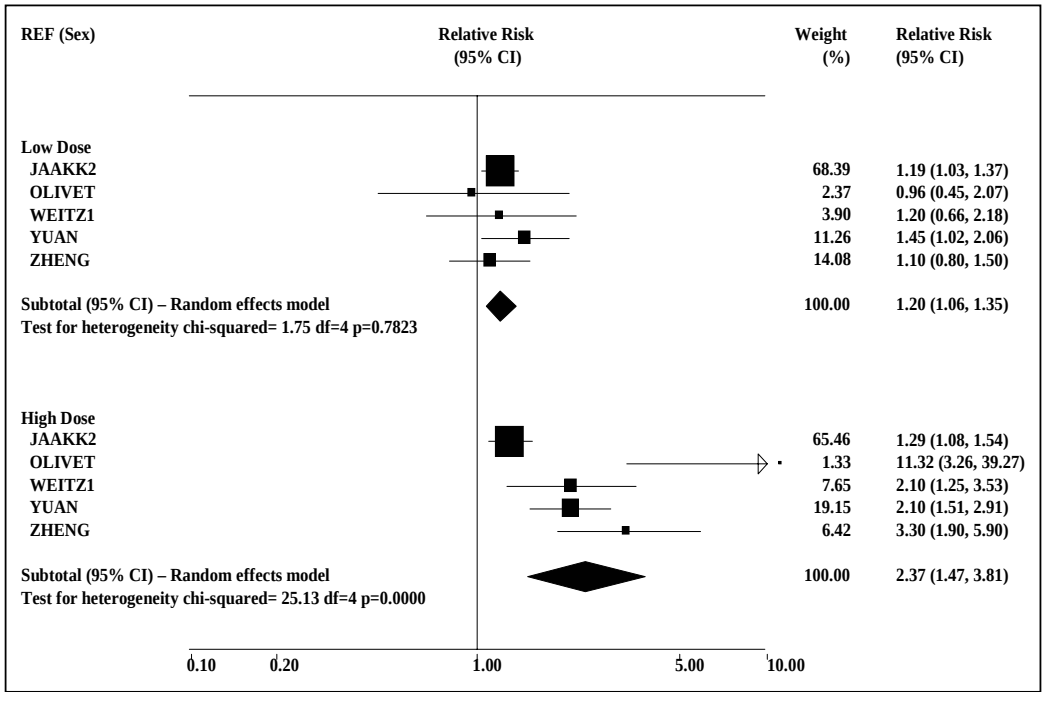

Figure 9.6. Forest plot for current/lifetime asthma and *in utero* exposure by amount – children.[1]

[1] Asthma outcome: current/lifetime; source of ETS exposure: maternal smoking or maternal ETS exposure in pregnancy; measure of dose: cigarettes or smokers; these terms are defined in §7.10.5. Data as used in Tables F1 and F2. The RRs used are adjusted for covariates where adjusted data are available.

Overall, the five low dose results give an estimate of 1.20 (1.06-1.35), without heterogeneity. The high dose results are heterogeneous ($p<0.001$) but clearly elevated whether fixed effects analysis (1.61, 1.39-1.86) or random effects analysis (2.37, 1.47-3.81) is used.

The results from study TAYLOR (noted above for the low and high doses respectively), and alternative "minutes per day" results from ZHENG are consistent with this pattern. Study XU found no significant difference between high and low dose exposure, but did not report any further details.

9.3.6. Separating Effects of In-life and *In Utero* Exposure – Table G and Appendix Table G

In order to separate the possible effects of in-life and *in utero* exposure, one requires studies for which separate RRs are available for in-life exposure only, *in utero* exposure only and both exposures combined relative to neither exposure. There are six such studies (AGABI1, AGABI2, CUNNI1, GILLIL, NHANE3, TARIQ). There are also two studies (HAJNAL, STERN2) providing RRs for combined vs neither exposure and one study (LOPEZC) providing an RR for in-life only vs neither exposure. As the results are of particular importance in interpreting the evidence on asthma induction in children we first summarize these nine studies briefly and then present the RRs (in Table 9.17) before describing the analyses based on them.

The Studies

AGABI1 and AGABI2

In 1994-1995 Agabiti et al. (1999) studied random samples of subjects aged 6-7 and 13-14 years in ten areas of Northern and Central Italy, with standardized questionnaires (ISAAC) completed by parents of 18737 children and 21068 adolescents about their smoking habits and the respiratory health of their children. The adolescents were asked about their respiratory health and personal smoking. Although conducted as a cross-sectional study, it was analyzed as a case-control study, with groups of cases with "current asthma" and with "current wheezing" not labelled as asthma compared to controls without respiratory symptoms or a past history of asthma. For the purposes of our analyses, the data for children and adolescents were considered separately as studies AGABI1 and AGABI2, and only the results for "current asthma" (history of asthma with wheezing symptoms in the last 12 months) were used. The source paper presents extensive information on the relationship between current asthma and maternal and paternal smoking, currently and at the time the mother was pregnant, with results adjusted for sex, age, urbanization level, father's education, household crowding, dampness or mould in the child's room, gas stove, gas boiler at home, parental asthma, other smokers at home, respondent to the questionnaire and, in the case of the data for adolescents, active smoking of the subject. Based on the results given in Table 3 jointly by maternal smoking in pregnancy and by smoking status of the mother (current, ex, never), it was possible to derive the required estimates for *in utero* only exposure, current exposure only and combined exposure, relative to neither exposure, shown in Table 9.17.

CUNNI1

In 1988-1990 Cunningham et al. (1996) studied the association of ETS with asthma and several measures of wheeze in schoolchildren aged 8 to 11 years in 24 communities in the US and Canada. Information on the child's respiratory symptoms in the past year and ETS exposure was provided by a parent on a questionnaire and analysis was restricted to the 11534 completed by the child's biological mother. No mention was made of smoking by the children. A variety of results were presented relating symptom prevalence to various indices of ETS exposure and parental smoking with adjustment for sex, race, parental education, household crowding, presence of a gas stove, home dampness, family income, community of residence, and parental history of respiratory illness. For the purposes of our main analyses, the results for "active diagnosed asthma" (ever diagnosed and experienced symptoms in last year) are used, although for combined *in utero* and in-life exposure results for an alternative definition of "medication for asthma" (ever diagnosed and taken medication in last year) are also considered. Table 4 of the paper presents the results (shown in Table 9.17) comparing children exposed in pregnancy only, after birth only, and at both times with those with neither exposure. It should be noted, however, that this analysis is restricted to those 5,799 children not currently exposed to ETS at the time of the study.

GILLIL

In 1993-1996 Gilliland et al. (2001) carried out a baseline study of the effects of maternal smoking during pregnancy and childhood ETS exposure in 5762 school-aged children resident in 12 Southern California communities. Responses to a self-administered questionnaire completed by parents of 4^{th}, 7^{th} and 10^{th} grade students were used to classify children as having wheezing or physician-diagnosed asthma, only results for the latter endpoint being considered here. Children were interviewed privately about their own smoking, and personal smoking was stated to be taken into account either by excluding ever smokers from analyses or by modelling personal smoking as a potential confounder, although for some of the analyses it is unclear which choice was made. Risks of lifetime asthma in those with ETS exposure only (exposure from any household member since birth), *in utero* exposure only and combined exposure were compared to those with neither exposure in males and females separately, with adjustment for town, grade, cohort and age. Similar comparisons were made for the sexes combined, with further adjustment for sex, race, hay fever, family history of asthma, family history of atopy and gestational age. Equivalent sexes combined results were also shown for current asthma (physician-diagnosed asthma with any asthma-related symptoms or illness in the past year) and for those taking medication for asthma. The various sets of odds ratios, taken directly from the source publication, are shown in Table 9.18. Asthma-free subjects from this study formed the baseline for a prospective study (MCCON1).

HAJNAL

In 1992-1993 Hajnal et al. (1999) conducted a cross-sectional study in 4470 schoolchildren in 10 communities in Switzerland. The children were in three age groups, 6-7, 9-11 and 13-14 years. ETS exposure, maternal smoking during pregnancy and respiratory symptoms were assessed by a self-administered parental questionnaire (ISAAC). Children who smoked were excluded from analysis. Results adjusted for sex, age, nationality, social

class, breastfeeding, family history of asthma, family history of bronchitis, family history of atopy, number of siblings, cooking fuel, floor type, pets and farming as the family profession were reported for a range of symptoms, including "asthma ever," and for a variety of indices of exposure, including combined exposure to maternal smoking, current and during pregnancy. No results were reported for exposure *in utero* only or in life only.

LOPEZC

López Campos et al. (2001) reported results from a case-control study in Lagunera, Mexico involving 58 allergic asthmatic children aged between 6 and 10 years and two controls for each case matched for age, sex and socioeconomic status drawn from a Family Medicine Clinic. Multiple choice questionnaires were given by GPs to the mothers. No mention was made of when the study was conducted or of smoking by the child. Analysis was carried out without adjustment for any variables, with ORs presented with a statement as to whether they were significant or not, with no CIs available. The ORs presented include one for maternal smoking outside pregnancy, which we have interpreted from the discussion in the paper as being for exposure in life only.

NHANE3

The NHANES III study was conducted from 1988 to 1994 by the National Center for Health Statistics at the Centers for Disease Control and Prevention. The survey uses a stratified multistage clustered probability design to select a representative sample of the civilian, noninstitutionalized US population. 81 geographic sites were included in the final sample. Questionnaires for participants younger than 17 years were completed by a knowledgeable proxy but children age 12 or more self reported tobacco use. Mannino et al. (2001) report results of an analysis limited to children aged 4 to 16 years for whom serum cotinine levels were obtained, excluding children who either reported current smoking or had cotinine levels higher than 113.6 nmol/L, indicative of possible current tobacco use. These were aimed at determining the effects of prenatal and postnatal smoke exposure on the respiratory health of children in the US. Results are presented relating to various symptoms including "ever asthma," based on a positive response to the question *"Has a doctor ever told you that your child has asthma?"*, and "current asthma" based on a positive response to the question *"Does your child still have asthma?"* Risks of the symptoms were related to cotinine tertile, and in a figure some results related to joint ETS and *in utero* exposure were presented for 4-6 year olds. These results compared children in the highest cotinine tertile (3.24 to 113.6 nmol/L) with prenatal maternal smoking (i.e. smoking in pregnancy), children in the lowest cotinine tertile (up to 0.59 nmol/L) with prenatal maternal smoking, and children in the highest cotinine tertile with no prenatal maternal smoking, with children in the lowest cotinine tertile with no prenatal maternal smoking. Adjustment was made for race/ethnicity, socioeconomic status, parental history of asthma and family size. The data (see Table 9.17) had to be estimated approximately from the figure. Similar results were not presented for children aged 7-11, it being noted only that the analysis "yielded no significant results." Some additional results for children aged <6 years, based on ETS exposure defined by whether any household member had smoked since birth, rather than by cotinine, are presented by Lanphear et al. (2001). These are adjusted for gender, race, poverty status, education of head of family, ever breastfed, received care in neonatal intensive care unit, birth weight, cat in home, urban residence and age house built.

Table 9.17. Individual relative risks for *in utero* and/or in-life exposure – children

Study(sex)	Used in Tables[2]	Asthma outcome	Source of in-life exposure[3]	Time of in-life exposure	RR (95% CI)[1]		
					Exposure *in utero* only	Exposure in-life only	Combined exposures
AGABI1	G1-G6	current	Mother	current	**1.72 (1.13-2.63)**	**1.05 (0.88-1.26)**	**1.52 (1.27-1.83)**
AGABI1	none	current	Mother	since birth[4]	-	1.18 (1.01-1.37)	-
AGABI2	G1-G6	current	Mother	current	**0.69 (0.45-1.05)**	**1.14 (0.99-1.33)**	**1.21 (1.02-1.45)**
AGABI2	none	current	Mother	since birth[4]	-	1.09 (0.96-1.25)	-
CUNNI1	G1-G6	current	Any Hh member	past[5]	**2.70 (1.13-6.45)**	**0.99 (0.78-1.25)**	**0.96 (0.63-1.48)**
CUNNI1	none	current[6]	Any Hh member	past[5]	2.03 (0.75-5.47)	1.04 (0.81-1.34)	1.02 (0.65-1.60)
GILLIL(m)	G1-G3	lifetime	Any Hh member	since birth	**1.70 (1.10-2.90)**	**1.00 (0.80-1.30)**	**1.10 (0.80-1.40)**
GILLIL(f)	G1-G3	lifetime	Any Hh member	since birth	**1.90 (1.10-3.50)**	**1.10 (0.80-1.40)**	**1.60 (1.20-2.20)**
GILLIL(c)[7]	none	lifetime	Any Hh member	since birth	1.80 (1.10-2.90)	1.10 (0.90-1.40)	1.30 (1.00-1.70)
GILLIL(c)	G4-G6	current	Any Hh member	since birth	2.30 (1.30-4.00)	1.10 (0.80-1.40)	1.30 (0.90-1.80)
GILLIL(c)	none	current[6]	Any Hh member	since birth	2.10 (1.20-3.60)	1.10 (0.80-1.40)	1.20 (0.90-1.70)
LOPEZC	none	current	Mother	ever	-	1.06 (NS)	-
NHANE3[8]	G1-G3	lifetime	Biochemical		**2.63 (0.30-25.12)**	**2.29 (0.91-5.01)**	**3.16 (1.10-9.12)**
NHANE3[8]	G4-G6	current	Biochemical		1.74 (0.30-11.48)	4.57 (1.38-13.80)	7.24 (2.51-20.89)
NHANE3[9]	none	lifetime	Biochemical		NS	NS	NS
NHANE3[9]	none	current	Biochemical		NS	NS	NS
NHANE3[10]	none	lifetime	Any Hh member	since birth	1.30 (0.60-3.00)	0.90 (0.60-1.30)	1.70 (1.20-2.50)
TARIQ	G1-G6	current	Mother	since birth	**1.58 (0.81-3.07)**	**0.98 (0.56-1.72)**	**1.21 (0.79-1.85)**
HAJNAL	G3,G6	lifetime	Mother	current	-	-	**1.31 (0.92-1.85)**
STERN2	G3	lifetime	Mother	first 2 years	-	-	**1.43 (1.09-1.88)**
STERN2	G6	current	Mother	first 2 years	-	-	0.98 (0.68-1.41)

[1] The estimates in bold are from Tables G1, G2 and G3. All estimates are adjusted for covariates where available. NS = not significant. - = not available.

[2] The estimates marked “none” are not used in any meta-analyses, either due to incomplete data, not selected by the preferences, or alternative disease outcome not included in database.

[3] Hh = household. Biochemical = highest vs lowest serum cotinine tertile.

[4] Using the definition of “parental smoking since birth,” estimates for “*in utero* only” and “both exposures” are not available because ex-smokers who smoked in pregnancy, irrespective of whether they also smoked in the child’s life, were considered together by the original authors.

[5] Excluding current exposure.

[6] Alternative definition of current asthma (ever diagnosed and taken medication in last year).

[7] Adjusted for sex and 5 additional confounders.

[8] Age 4-6.

[9] Age 7-11.

[10] Age 0-5.

STERN2

Stern et al. (1989b) reported results from a cross-sectional study of 4003 Canadian schoolchildren aged 7 to 12 years in 10 communities in Ontario and Saskatchewan. Parents completed a self-administered questionnaire on respiratory health, smoking, home characteristics, education and parental respiratory health. No mention was made of when the study was conducted or of smoking by the child. Crude ORs were presented for various endpoints, including doctor diagnosed asthma and doctor diagnosed asthma in the previous year, relating to exposure to maternal smoking during both pregnancy and the first two years of life. Adjustment for the effects of parental education, parental respiratory illness history and gas cooking in the home was stated not to significantly alter the rates. No results were presented for *in utero* exposure only, or in life exposure only. Slightly different results had been reported earlier (Stern et al., 1987).

TARIQ

A number of publications have described results from a cohort of all births in the Isle of Wight, England in 1989-1990 recruited soon after birth. Those who remained resident on the Isle of Wight were followed up at ages 1, 2, 4 and 10 years, and information on parental and other household smoking was updated. In the report of Tariq et al. (2000), which is the only one to consider joint effects of *in utero* and in-life exposure, current asthma at age 4 was defined as 3+ episodes of cough and wheeze per year each of 3 days or more, and data were only considered on maternal smoking, either in pregnancy or after childbirth. RRs were not presented by the authors but sufficient detail was provided to calculate crude RRs for smoking in pregnancy only, and combined exposures compared to smoking at neither time.

Note that studies are considered in this section if, in their analysis, they considered *in utero* exposure and in-life exposure separately. Some other studies found no smoking mothers (AZIZI, CHEN1) or very few smoking mothers (e.g. QIAN, ZHANG), or excluded smoking mothers (SHIVA, VENNER) or mothers who smoked in pregnancy (MILLER), so that their results may be relevant to the comparison of in-life only exposure versus no exposure either in-life or *in utero*, but they are not considered here. Nor are results relevant to ETS exposure of the mother during pregnancy considered here.

The Data

Table 9.17 presents the individual RRs for *in* utero and/or in-life exposure available from the nine studies described above. In all the studies, *in utero* exposure refers to smoking by the mother during pregnancy. However the definitions of in-life exposure vary. This is relevant even where the comparison is between *in utero* only exposure and neither exposure, in that only subjects unexposed according to the specified definitions are included in the comparison. Thus for studies AGABI1 and AGABI2, where in-life exposure was defined as maternal smoking currently, and for study NHANE3 where in-life exposure was biochemically assessed (and is thus intrinsically current), the "*in utero* only" group and the "neither exposure" group may contain children with past in-life exposure. Similarly, for AGABI1, AGABI2 and TARIQ, where the in-life exposure refers to exposure from the mother, the unexposed groups may contain children with paternal exposure. Further, for study CUNNI1, the analysis excludes children with current exposure and refers only to past in-life exposure.

Also, for study NHANE3, the exposure is defined as highest vs lowest tertile serum cotinine (there being no results available for the middle tertile), and children with levels above 113.6 nmol/L were excluded as being likely smokers.

Table 9.17 shows that there are six studies that provide data for *in utero* exposure only, seven that provide data for in-life exposure only, and eight for combined exposure. Only one study (GILLIL) provides sex-specific estimates. Where estimates are available for all three exposure definitions, the RRs tend to be highest for *in utero* only and lowest for in-life only. Thus, of the 13 (non-independent) sets of three estimates, there are nine where the highest estimate is for *in utero* only exposure and nine where the lowest is for in-life only exposure and 11 where the *in utero* only exposure exceeds that for in-life only exposure. Exceptions to the general pattern are the AGABI2 and NHANE3 studies, the latter having estimates with much wider CIs that other studies. The pattern is assessed more formally in the section that follows.

Meta-analyses

Tables G1, G2 and G3 present the results of meta-analyses for the three types of exposure (*in utero* only, in-life only, both) for the following preferences: asthma outcome = lifetime/current, and in-life element of exposure/non-exposure = Biochemical/Household (overall)/Parent (mother). Tables G4, G5, G6 repeat the sequence but with the asthma outcome preference chosen as current/lifetime.

Table 9.18 summarizes the results of the adjusted meta-analyses. Also included are revised versions of Tables G3 and G6 based only on the same group of six studies considered in the other tables.

It can be seen that the analyses generally show a significant ($p<0.05$) increase in risk of asthma associated with *in utero* only exposure, or with exposure in life and *in utero* but not with in-life exposure only.

The estimates for Tables G4, G5 and G6 based on current/lifetime asthma are very similar to those for Tables G1, G2 and G3 based on lifetime/current asthma. For five of the eight studies, the data included are in fact identical, with separate estimates for lifetime and current asthma only being available for the GILLIL, NHANE3 and STERN2 studies. The estimates for Tables G3 and G3R and for Tables G6 and G6R are also very similar. Thus the pattern of results is not materially dependent on the precise definition of asthma outcome used or whether or not attention is restricted to the six studies that give the full set of estimates.

For the estimates included in Tables G1, G2 and G3, based on the preference lifetime/current, it should be noted that the variance of the estimates for exposure *in utero* only is larger (weight = 85) than it is for exposure in life only (496) or exposure at both times (459). The studies AGABI1 and AGABI2 together have about half the total weight for each exposure (totalling 43, 296 and 239 respectively) while the weights for the cotinine based NHANE3 study are particularly small (0.8, 5.3 and 3.4 respectively).

For exposure *in utero* only, the meta-analysis shows evidence of heterogeneity (χ^2_{het} = 15.93 on 6 d.f., $p<0.05$) due to the unusually low RR in the AGABI2 study (0.69, 0.45-1.05, Q_s = 11.01). However, the other six RRs are all greater than 1.00 (indeed all are in the range 1.58 to 2.70) with four being statistically significant (at $p<0.05$), and both the fixed effects estimate (1.41, 1.14-1.75, $p<0.01$) and the random effects estimate (1.53, 1.05-2.23, $p<0.05$) are statistically significant.

Table 9.18. Summary of analyses of *in utero* and/or in-life exposure – children

Table	Exposure	Asthma outcome[1]	N[2]	Fixed effects RR (95% CI)[3]	Random effects RR (95% CI)[3]	Heterogeneity Chisq per df[4]
G1	*In utero* only	L/C	7	1.41 (1.14-1.75)	1.53 (1.05-2.23)	2.66*
G2	In-life only	L/C	7	1.08 (0.99-1.18)	1.08 (0.99-1.18)	0.77 N.S.
G3	Both	L/C	9	1.33 (1.21-1.46)	1.32 (1.18-1.49)	1.46 N.S.
G3R[5]	Both	L/C	7	1.32 (1.19-1.46)	1.31 (1.12-1.53)	1.89(*)
G4	*In utero* only	C/L	6	1.40 (1.11-1.77)	1.57 (0.97-2.52)	3.40**
G5	In-life only	C/L	6	1.09 (0.99-1.20)	1.09 (0.96-1.24)	1.45 N.S.
G6	Both	C/L	8	1.30 (1.17-1.43)	1.29 (1.07-1.55)	2.56*
G6R[5]	Both	C/L	6	1.33 (1.19-1.48)	1.35 (1.07-1.70)	3.09**

[1] Asthma outcome: L/C = lifetime/current, C/L = current lifetime, defined in §7.10.5.
[2] N = number of RR estimates combined.
[3] The RRs used are adjusted for covariates where adjusted data are available.
[4] Significance of heterogeneity: *** p<0.001, ** p<0.01, * p<0.05, (*) p<0.1, NS p>0.1.
[5] Omitting studies HAJNAL and STERN2 for which *in utero* only and in-life only estimates were not available.

For the data for exposure in life only, the results are generally consistent with a lack of association with asthma. None of the seven estimates are statistically significant (at p<0.05), there is no significant heterogeneity (χ^2_{het} = 4.64 on 6 d.f., p≥0.1) of the RR (1.08, 0.99-1.18), and most of the estimates are close to 1.0. The apparently higher estimate of 2.29 from the NHANE3 study is highly variable (95% CI 0.91-5.01), and is less suggestive of a possible increase than that for the largest, AGABI2, study where the RR of 1.14 (0.99-1.33) is close to significance.

For combined exposures, on the other hand, all but one of the nine estimates are greater than 1.0, and five are statistically significantly increased at p<0.05. The fixed effects RR (1.33, 1.21-1.46) shows no significant heterogeneity (χ^2_{het} = 11.64 on 8 d.f., p≥0.1). Comparing the results for both exposures with those for exposure *in utero* only there is no tendency for both exposures to show higher RRs. Indeed for five of the seven studies the RR for both exposures is lower.

Generally, the pattern of no increase in risk for exposure in life only and an increase for exposure *in utero* only and for both exposures seems reasonably clear, given the variability of the data. The principal exception is the AGABI2 study.

The data considered from Tables G1, G2 and G3 are for RRs adjusted for covariates where possible, with seven of the nine studies having adjusted data. Results based on RRs unadjusted for covariates where possible are very similar and confirm the general pattern of a lack of association of asthma with in-life exposure, whether considered on its own, or as a part of both exposures (compared to *in utero* exposure on its own).

For the estimates included in Tables G4, G5 and G6, based on the preference current/lifetime, differences, compared to the corresponding Tables G1, G2 and G3, come from the GILLIL, NHANE3 and STERN2 studies. The very high RRs seen in the NHANE3 study for exposure in life only (4.57, 1.38-13.80) and for both exposures (7.24, 2.51-20.89) stand out as different. For exposure in life only, the overall heterogeneity statistic is not significant (χ^2_{het} = 7.26 on 5 d.f.), due mainly to the remarkable similarity of the other five estimates (0.98, 0.99, 1.05, 1.10, 1.14) and the low weight of the NHANE3 estimate (3 out of a total of 429 for all the studies). However the NHANE3 result certainly seems unusual, having a lower 95% confidence limit of 1.38 and a Q_s of 5.95. For combined exposures, there is more evidence of heterogeneity (χ^2_{het} = 17.90 on 7 d.f., $p<0.05$), with the NHANE3 estimate having a Q_s of 10.12 and a lower 95% confidence limit of 2.51, higher than the largest upper 95% confidence limit seen for any of the other eight estimates. The NHANE3 study results are very different from the other studies, suggesting an important role of in-life exposure, not indicated by the other studies. It should be remembered however that, for the NHANE3 study, RRs were only available for children aged 4-6 years. No significant effects of exposure were seen in the corresponding analyses for the age group 7-11 years, but RRs were not reported.

Table 9.17 also shows various other RR estimates not included in the meta-analyses. Generally, these show an increase in risk associated with exposure *in utero* only (only significant for the GILLIL study), and an estimate close to 1.00 and no significant association with exposure in life only. Exceptionally, for study AGABI1 with exposure from the mother since birth, there is a marginally significant increase (1.18, 1.01-1.37) associated with exposure in life only.

Effect of Adjusting In-life Exposure Estimates for In Utero Exposure

To further investigate the joint effects of in-life and *in utero* exposures, studies other than those included in Table G which presented equivalent results for in-life exposure both unadjusted and adjusted for *in utero* exposure were examined. The available data are summarized in Table 9.19.

Only in one study (DIJKST) are the definitions of the RRs identical apart from the *in utero* adjustment. However, the adjusted result, described in the original paper as *"somewhat attenuated,"* is incomplete.

Most of the comparisons are between an unadjusted RR and a multiply-adjusted RR, where *in utero* exposure is just one of a number of factors adjusted for. Full data are available only for five comparisons, in none of which the significance altered, with two (HABY and SOYSET-mother) showing an increased RR, one (HU1) showing a decreased RR, and two (SOMERV-boys and SOMERV-girls) showing little apparent effect of adjustment. The partial data available for the other comparisons are not suggestive of any change.

Table 9.19. Selected relative risks for in-life exposure – children

Study (sex)	Asthma[1]	Definition of in-life exposure	Unadjusted for *in utero* exposure		Adjusted for *in utero* exposure	
			Other adj[2]	RR/CI	Other adj[2]	RR/CI
DIJKST	c	household – current	0	1.95 (0.91-4.19)	0	NS
			12	1.77 (no CI)		
HABY	c	any parent – age <6m	0	1.34 (0.97-1.85)	8	1.62 (0.95-2.75)
HU1	l	mother – current	0	1.22 (0.78-1.89)	6	0.80 (0.50-1.50)
SOMERV(boys)	c	any parent – current – per cigarette	1	0.99 (0.97-1.01)	10	1.00 (0.97-1.02)
SOMERV(girls)	c	any parent – current – per cigarette	1	1.02 (1.00-1.04)	10	1.03 (1.00-1.05)
SOYSET	1	mother – since birth	0	1.99 (1.08-3.67)	4	2.80 (1.30-6.10)
	l	father – since birth	0	1.52 (0.84-2.75)	5[3]	NS
STAZI	l	mother – since birth	2	NS	6	NS
		mother – current	2	NS	6	NS
		father – since birth	2	NS	6	NS
		father – current	2	NS	6	NS

[1] Asthma: c = current, l = lifetime.
[2] "Other adj" gives the number of other factors for which adjustment was made.
[3] Includes adjustment for maternal smoking since birth.

Table 9.20. Selected relative risks for *in utero* exposure – children

Study	Asthma[1]	Unadjusted for in-life exposure		Adjusted for in-life exposure		
		Other adj	RR/CI	Definition of in-life exposure	Other adj[2]	RR/CI
HABY	c	0	1.19 (0.81-1.74)	Either parent smoked in first 6 months	8	0.77 (0.40-1.48)
HU1	l	0	1.76 (1.11-2.79)	Current maternal smoking	6	1.90 (1.10-3.50)
NILSSO	l	0	1.40 (1.00-2.00)	Current parental smoking	6	1.30 (0.80-1.90)
SOYSET	l	0	1.26 (0.71-2.25)	Maternal smoking since birth	7	0.60 (0.30-1.30)

[1] Asthma: c = current, l = lifetime.
[2] "Other adj" gives the number of other factors for which adjustment was made.

Effect of Adjusting In Utero Exposure Estimates for In-life Exposure

The available data for studies which presented equivalent results for *in utero* exposure, both unadjusted and adjusted for in-life exposure, apart from those included in Table G, are summarized in Table 9.20.

Again, the comparisons are between an unadjusted RR and a multiply-adjusted RR. For three of the studies adjustment decreased the RR, losing its borderline significance in one (NILSSO), and dropping well below 1.00 in two (HABY, SOYSET) although they remain non-significant. In the remaining study (HU1) adjustment increased an already significant RR.

9.4. DISCUSSION

9.4.1. Evidence of an Association

As can be seen from Table 9.12 for in-life exposure and Table 9.15 for *in utero* exposure, there is a highly significant association between current or lifetime asthma and various indices of exposure to smoking by parents or other household members. However, though statistically significant, the associations are not strong. For example, random effects estimates based on covariate adjusted RRs are 1.23 (1.17-1.29) for total in-life exposure (or nearest equivalent) for lifetime asthma, 1.20 (1.13-1.27) for total in-life exposure for current asthma, and are 1.31 (1.19-1.45) for *in utero* exposure for lifetime/current asthma. Associations for in-life exposure tend to be strongest where both parents smoke and stronger in relation to maternal than paternal smoking. Indeed, when the father only smokes no significant elevation in risk is seen, with an estimate of 1.11 (0.96-1.29) for lifetime asthma based on only five studies.

9.4.2. Evidence of a Dose-response Relationship

Evidence of a dose-response relationship has been investigated in various ways in the studies considered, most commonly by number of cigarettes per day and by number of persons in the household who smoke. For in-life exposure, the results in Table D and §9.3.3 show clearly that RRs associated with high dose total exposure are substantially greater than those associated with low dose total exposure – for example for lifetime asthma random effects estimates are 1.39 (1.16-1.68) for high exposure and 1.07 (0.93-1.22) for low exposure based on the 19 pairs of RRs included in the meta-analyses in Tables D1 and D2. These findings seem generally to be supported by the results of other studies that provided results in terms of risk per unit dose, and could not be simply included in the categorical low dose/high dose analyses. For *in utero* exposure only five studies could be identified which provided pairs of low dose and high dose estimates. However, as discussed in §9.3.5, the limited data strongly support a dose-response relationship, with random effects estimates 2.37 (1.47-3.81) for high exposure, where all five studies individually show significant increases, and 1.20 (1.06-1.35) for low exposure, with only two studies showing significant increases.

Clearly, the data available show an association and a dose-response relationship that, at least for a number of the exposure indices, cannot be explained by chance. In order to interpret these findings it is necessary to consider various aspects of the data further.

9.4.3. Consistency of Findings

As seen, for example, in Table 9.12 (in-life exposure) and Table 9.15 (*in utero* exposure), there is statistically significant heterogeneity for a number of the exposure indices studied. Identifying the sources of the heterogeneity is not straightforward, partly because in some meta-analyses (e.g. Tables C1 and C3) particular studies (notably LEE3, STURM and WANG) have a very large weight and a risk estimate somewhat different from the remaining studies, for reasons that are not clear. Also, for some exposure indices, the number of estimates available is too small to allow detailed study of sources of heterogeneity.

We have only investigated variation in risk by one factor at a time rather than on a multivariate basis. However, looking at some of the key analyses (Table C1 – total exposure/lifetime asthma, Table C3 – total exposure/current, Table C5 – parent/lifetime, Table C7 – parent/current, Table C45 – mother/lifetime, Table C47 – mother/current, Table E1 – *in utero*/lifetime), some overall impressions can be gained from these univariate analyses. Firstly, it is clear that for many of the factors considered there is little or no evidence of meaningful heterogeneity, with RR estimates generally greater than 1.0 for each factor level. Second, there is no one factor that explains a substantial part of the heterogeneity. However, there are some factors for which comment seems merited.

Country in Asia. Although significant heterogeneity was not found in all the analyses, it is in general true that studies conducted in the Far East (China, Japan, Hong Kong, Taiwan and Korea) showed little or no association of asthma with exposure.

Timing of study. In the analysis of current asthma (C3, C7), the few studies starting before 1980 or published before 1990 show no increase in risk. This variation is not evident in the analyses of lifetime asthma (C1, C5).

Study type. RR estimates are in general elevated for all the three study types. The tendency is for estimates to be highest in case-control studies, particularly for current asthma (C3, C7).

Age. RR estimates are in general elevated for children in all age groups. The estimates are usually highest for the children aged 0-9, except for lifetime asthma and maternal smoking (C45).

Child the respondent. In the analyses of in-life exposure for lifetime asthma (C1, C5), RR estimates tend to be lower (though still above 1.0) when the child was the respondent for questions on either ETS exposure or diagnosis of asthma. The pattern is not evident in the analyses of in-life exposure for current asthma (C3, C7). The child was rarely the respondent in studies of the effects of *in utero* exposure.

Child smoking. In the analyses of in-life exposure (C1, C3, C5, C7) there is a consistent tendency for risk estimates to be relatively low (though still above 1.0) in studies where steps had been taken to exclude children who smoked. Interestingly, the reverse is true for *in utero* exposure (E1), with risk estimates relatively high in such studies.

Questionnaire used. In the analyses of in-life exposure for lifetime asthma (C1, C5) RR estimates are relatively low where the ISAAC questionnaire was used. In contrast risk

estimates were relatively high using the ISAAC questionnaire for current asthma. The questionnaire showed no relationship in the *in utero* analyses.

Given the variability in study methodology, it would be expected that associations observed would show some evidence of heterogeneity. However, the prevailing impression of the analyses is that where a positive association is present in the overall data, it is also seen in subsets of the data divided by levels of virtually every factor that has been investigated, with Far East studies being the only subset consistently not exhibiting evidence of an association. Though there is some evidence, as noted above, that the magnitude of the association may vary by some factors, this does not affect the impression of a highly consistent association.

9.4.4. Publication Bias

As noted in §8.4.4, there are various potential causes of a consistent association with a dose-response relationship, other than a cause and effect relationship. Publication bias is one source of bias to be considered. When the traditional main sources of publication bias (see §8.4.4) were tested for by Egger's method (Egger et al., 1997) it was generally found not to be significant. Thus, of the 90 meta-analyses of covariate adjusted data in tables C to G, only nine show evidence of publication bias significant at least at $p<0.05$, with only four of those nine significant at $p<0.01$. While slightly greater than the number of significant findings expected by chance based on 90 analyses (4.5 at $p<0.05$ and 0.9 at $p<0.01$), this does not provide strong evidence of publication bias. Though one cannot exclude the possibility of some publication bias of this type existing, it seems unlikely to explain more than a minor part of the association. This is in any case evident from the large proportion of statistically significant positive associations seen in some analyses. For example, the analyses of lifetime parental exposure (Table C5) include 72 RR estimates, of which 25 are significantly greater than 1.0 and one significantly less than 1.0. One would need to have about 1000 studies before one would expect to see by chance 25 positive associations significant at $p<0.05$. One would hardly expect that these unpublished studies, if they existed, would produce the compensating number of significant negative associations required to make the total data (published and unpublished) consistent with no overall relationship.

However, another form of publication bias needs to be considered in studies of this type. Authors may publish a paper, and then carry out a large number of analyses relating to a variety of exposures and endpoints, only reporting fully the more "interesting" findings. One cannot properly assess the extent of this sort of bias without access to the source data. However, some insight into the problem can be gained by comparing the frequency of statistically significant results in the findings included in the meta-analyses with the corresponding frequency in findings that were not reported in enough detail to be included. For in-life exposure, the meta-analyses in Tables C1 and C3 together provide 197 RRs, of which 49 (29.9%) are statistically significant. This can be compared with only 4[21] out of 36 incompletely published RRs (11.1%), a difference which is close to statistical significance ($0.05<p<0.1$). For *in utero* exposure, Table E1 provides 32 RRs of which 12 (37.5%) are

[21] Assuming that the three relative risks in the RUDNIK study for which the value, but not the significance, was given were actually not significant. See §9.3.2 for more details.

significant. Here too the frequency of significant results amongst those which are incompletely published (2/8 = 25.0%) is non-significantly lower.

These findings demonstrate that there are certainly quite a number of studies that could provide data suitable to be included in meta-analyses, but which have not done so. They also suggest that, were these additional results available for inclusion, RR estimates might have decreased slightly. However, they still do not suggest that publication bias is a major issue in interpretation.

9.4.5. Diagnostic Bias

As noted in §8.4.5, an epidemiological study should ideally involve a disease with a clearly defined and accepted definition, with subjects diagnosed accurately. However, clinical definitions of asthma vary, as is evident from the substantial variations observed in the frequency of the disease among children (National Cancer Institute, 1999). Here we specified that only studies where the endpoint was "asthma" were to be included, with studies of "wheeze," "wheezing bronchitis" or "chronic wheezing," and also "asthma or wheeze" and "asthmatic bronchitis," to be excluded. While this distinction was not always clear-cut and, as discussed further in §7.1, may have led to some anomalies, it seems likely to us that the great majority of the results we consider relate to conditions which are at least quite similar and which might be expected to have a similar relationship to ETS exposure and smoking during gestation.

In the 134 studies which provided results for lifetime asthma, the diagnosis was taken from medical records, or was made by a physician in the course of the study design, in 14 (10%), with the diagnosis made by a physician but reported by the parent and/or the child in 63 (47%). In the remaining 57 (43%), asthma was at least partly based on the parent's or child's own assessment rather than physician diagnosis. In the 105 studies which provided results for current asthma, the corresponding frequencies were 22 (21%) for medical records/physician diagnosis, 16 (15%) for diagnosis made by physician but reported by child or parent and 67 (64%) for diagnosis involving parent's or child's assessment.

When testing for heterogeneity according to physician diagnosis, comparison was made between those studies that only involved physician diagnosis (regardless of who reported it) and those studies that were based wholly or partly on child or parent assessment. In the main analyses of in-life exposure (Tables C1, C3, C5, C7), there is no evidence of any difference between the RR estimates for these two groups of studies. In the analysis of *in utero* exposure (Table E1) there is, however, some evidence ($p<0.05$) of a higher RR estimate in the physician diagnosed group of studies, where the random effects estimate is 1.40 (1.22-1.61, n = 16) as compared to 1.23 (1.08-1.41, n = 16).

Tests were also made for heterogeneity according to the source of information about the diagnosis. In the main analyses of in-life exposure, there is quite consistent evidence of heterogeneity, with risk estimates lower when the child was the respondent than where the asthma diagnosis was based on medical records. Thus, in Tables C1, C3, C5 and C7, the RR (random effects) associated with the child as the source was in the range 1.05 to 1.18, while that associated with medical records as the source varied between 1.27 and 1.43, with the heterogeneity significant or near significant in all the analyses. Where the parent was the source, the RR estimates also tend to be lower than where the medical records were, but only

to a much smaller extent. For *in utero* analyses, the parent was nearly always the source of the diagnosis and tests of heterogeneity are not very sensitive.

Generally, these analyses suggest that RR estimates are higher where the asthma diagnosis was based on physician diagnosis and derived from medical records than when the diagnosis was made or reported by the child or parent. If one can assume that physicians can diagnose asthma more accurately, these observations are consistent with the presence of some diagnostic bias. It should be noted that the child was more often the respondent in studies using the ISAAC questionnaire than in other studies (38% vs 7% for lifetime asthma, 48% vs 10% for current asthma).

9.4.6. Representativeness

It is clear that the children included in a study may not necessarily be completely representative of all the children in the population of interest. This may arise because the study is deliberately conducted in a particular subgroup (e.g. a specific school), because of unwillingness of certain children (or their parents or doctors) to participate in the study, or because of study design requirements (e.g. that the child lives with both parents). In some studies, unrepresentativeness might also arise in the selection of cases with asthma, perhaps because some children (or their parents) do not report past or present symptoms to a doctor, so that a diagnosis of asthma is never made. Unrepresentativeness may lead to errors in estimation of the frequency of exposure or of the frequency of disease in the population, but this will not necessarily cause any bias in the estimated RR associated with exposure. However, if there is marked variation in the RR in different subsets of the population, lack of representativeness can cause selection bias. The results discussed under “consistency of findings” in §8.3 above suggest, however, that such marked variation in the RR across subsets of the population does not occur. As such, it seems unlikely that simple unrepresentativeness is a major issue.

However, unrepresentativeness may be an issue if one or more causes of unrepresentativeness are linked to both exposure and asthma. For example, if, in a cross-sectional study, non-responders tend to be more (or less) likely to be asthmatics with smoking parents, the observed relationship between asthma and parental smoking would clearly be weaker (or stronger) than that which actually existed. Similarly, if parents who smoke are more (or less) likely to draw attention to their child’s asthma to a doctor, a case-control study based on doctor-diagnosed cases may over- (or under-) estimate the true association of asthma with parental smoking. Accurate estimation of the extent of possible bias from such sources is not possible. Data on the extent of non-response are often not reported in the source papers and for this reason have not at this stage been collected in the database. Information on the extent of undiagnosed asthma and its relationship to ETS exposure would be difficult to assess.

All one can do is note that studies conducted in various settings and by various epidemiological techniques have consistently shown an association of asthma with exposure to ETS or maternal smoking during pregnancy, and that the specific sources of bias noted above do not seem likely to these authors to be major.

9.4.7. Misclassification of Exposure

In the analyses of total in-life exposure in Table C1 (lifetime asthma) and Table C3 (current asthma), only four of the 197 RR estimates (2.0%) are based on biochemical measurement. In the analyses of *in utero* exposure in Table E1, none of the 32 RR estimates are based on biochemical measurement. It is clear that virtually all the estimates depend on data reported, typically by a parent, on smoking by the mother, father or other household members. Though reported data are generally highly reliable, there is ample documentation that a small proportion of smokers deny smoking on interview (Lee & Forey, 1995) and also that reporting of a child's smoking by a parent is not completely accurate. Random misclassification of exposed children as unexposed (or of unexposed children as exposed) will tend to lead to some underestimation of the true association of exposure with asthma. However, misclassification may not necessarily be random. If having a child with asthma makes it more likely that ETS exposure will be reported (perhaps because the respondent is trying to explain the child's condition), then the RR will be overestimated. If, on the other hand, parents with an asthmatic child tend to be less likely to report their smoking (perhaps out of guilt), then the RR will be underestimated.

The magnitude and direction of any bias is difficult to determine with certainty, but it seems likely that any effect of misclassification of exposure will be to somewhat underestimate the true association.

9.4.8. Smoking by the Child

Assuming that the smoking habits of family members tend to be correlated, as has been demonstrated for husbands and wives (Lee, 1992) and some studies of parents and children (US Surgeon General, 1994), a child who smokes is more likely than a non-smoking child to be ETS exposed at home and to have a mother who smoked in pregnancy. If smoking increases the risk of asthma, as has been claimed by some (e.g. Larsson, 1994; Beeh et al., 2001), it would then be expected that some of the observed association between asthma and exposure to ETS or exposure during gestation would arise as a result of confounding by smoking by the child. This would not explain the association between ETS and asthma seen in children less than 10 years of age, since virtually no children of that age smoke. It is also unlikely to be a major source of bias for somewhat older children where the proportion who smoke will be relatively small. Also, some of the researchers took pains to exclude smokers from their study.

Although these considerations would suggest little bias to the overall association due to smoking by the child, it is interesting that, as noted in §9.4.3, the main in-life analyses (but not the *in utero* analyses) show a consistent tendency for RR estimates to be relatively low in studies where smokers had been excluded. For example, in Table C1, RR estimates (random effects) are 1.26 (1.10-1.44, n = 9) where child smokers had knowingly been included, 1.25 (1.17-1.32, n = 79) where the problem of child smoking had been ignored, and 1.12 (1.02-1.22, n = 22) where child smokers had been excluded or where there were found to be no child smokers, with the heterogeneity chisquared 7.40 on 2 d.f. ($p<0.05$). A similar pattern is also evident in a further analysis (data not shown) limited to studies which included at least some children of age 15 years or older. Here the RR estimates (random effects) are 1.29

(1.13-1.47, n = 8) where child smokers had been included, 1.29 (1.12-1.50, n = 21) where the problem had been ignored, and 1.07 (0.97-1.19, n = 15) where child smokers had been excluded, with the heterogeneity chisquared 11.60 on 2 d.f. ($p<0.01$).

9.4.9. Confounding

As for the studies in adults (see §8.4.9), a wide range of potential confounding variables have been taken into account in at least some of the studies considered. Apart from other sources of exposure to tobacco smoke or its constituents, factors quite commonly considered (in at least 20 studies) include the sex, age and race of the child, location within the study area (including urban/rural residence and indices of air pollution), the medical history of the child (including breastfeeding and skin prick test results), the medical history of the family (including history of asthma, allergy or other respiratory symptoms), SES (or parental education), household composition (number of children, single parent, position in sibship, etc), cooking and heating methods (including use of incense and mosquito coils), damp or mould in the home, aspects of housing quality (including age, size, crowding, use of shared bedroom, owned/rented) and close contact with animals (including pets in the home). However, some other factors that might be considered important, such as diet, exercise, use of day care and use of air conditioning and humidifiers, have only rarely been considered. For example, only two studies took diet into account.

As discussed in more detail in §8.4.9, there are considerable problems in assessing the extent of confounding, particularly by individual variables. The statistical analyses we conducted look at the issue of confounding using four methods:

A) alternative analyses are conducted using adjusted RRs where possible and unadjusted RRs otherwise, or using unadjusted RRs where possible and adjusted RRs otherwise;
B) within a given analysis, RR estimates are compared according to the number of adjustment variables taken account of (0, 1, 2, 3-5, 6-9 or 10 or more);
C) within a given analysis, RR estimates are compared according to whether or not the *study* took into account each of a specified list of potential confounding variables (sex; age; race; location; SES; family medical history; family composition; cooking, heating or air conditioning; housing quality, crowding, damp or mould; pets, animal contact or farming; or child's medical history); and
D) within a given analysis, RR estimates are compared according to whether the *RR* took into account a shorter specified list (sex; age; other ETS; any other factor).

Table 9.21 summarizes the results from method A, for a number of the more important analyses. As can be seen, there is some tendency for RR estimates to be lower in the adjusted analyses. In eight of the 11 selected Tables, the adjusted estimates are lower, the difference being largest for Tables E1 (0.07), C7 (0.06) and C47 (0.06). In two, Tables C53 and D1, the estimates are the same to two places of decimals and in one, Table D2, the estimate is slightly higher, by 0.01. Note, however, that the adjusted and unadjusted estimates include many RRs common to both the analyses compared – either because only unadjusted or only adjusted RRs are available for some studies.

Table 9.21. Comparison of adjusted and unadjusted relative risks – children

Table	Asthma outcome	Exposure source	No of estimates[1]	Adjusted[2] RR (95% CI)	Unadjusted[3] RR (95% CI)	Estimates differing[4]
C1	Lifetime	Total	110	1.20 (1.17-1.23)	1.21 (1.18-1.24)	43
C3	Current	Total	87	1.17 (1.15-1.20)	1.20 (1.18-1.23)	28
C5	Lifetime	Parent	72	1.27 (1.23-1.32)	1.28 (1.24-1.32)	29
C7	Current	Parent	45	1.21 (1.14-1.28)	1.27 (1.20-1.34)	15
C45	Lifetime	Mother	49	1.30 (1.25-1.35)	1.31 (1.26-1.35)	26
C47	Current	Mother	29	1.21 (1.14-1.29)	1.27 (1.20-1.34)	12
C53	Lifetime	Father	35	1.18 (1.13-1.22)	1.18 (1.14-1.23)	8
C55	Current	Father	24	1.04 (0.97-1.10)	1.06 (1.00-1.13)	8
D1	Lifetime	Total: low	19	0.95 (0.89-1.02)	0.95 (0.89-1.01)	6
D2	Lifetime	Total: high	19	1.22 (1.10-1.36)	1.21 (1.11-1.33)	6
E1	Lifetime/ current	*In utero*	32	1.28 (1.21-1.35)	1.35 (1.29-1.42)	18

[1] For Tables C1, C5 and C45 the number of unadjusted estimates is slightly higher as some studies provided sex-specific unadjusted results.

[2] Fixed effects estimate using RRs adjusted for covariates where possible, and unadjusted RRs otherwise.

[3] Fixed effects estimate using RRs unadjusted for covariates where possible, and adjusted RRs otherwise.

[4] Number of estimates for which separate adjusted and unadjusted RRs are available.

Perhaps a more useful test of adjustment is the method B analysis where the "adjusted" RRs are separated according to the number of variables actually taken into account. Thus, for example, in Table C1 (Lifetime asthma, total exposure), of the 110 RRs considered, 53 are adjusted for no variables at all, while 14, 6, 14, 18 and 5 are adjusted, respectively, for 1, 2, 3-5, 6-9 or 10+ variables. Table 9.22 summarizes the results of the method B analyses conducted.

The analyses for total lifetime exposure (Tables C1 and C3), parent smoking (C5 and C7) and smoking by the mother (C45 and C47) generally show little evidence of trend or heterogeneity of risks by number of adjustment variables. As discussed in §9.3.2, the significant heterogeneity for Table C1 partly reflects a single study (LEE3, which adjusted for no variables) with very large weight having a quite low RR. The trend in that analysis, though nominally significant ($p<0.05$), is clearly not linear, explaining little of the heterogeneity. There is perhaps more evidence of an effect of adjustment in the analyses of smoking by the father (C53 and C55). In Table C53 (lifetime asthma), the heterogeneity is significant ($p<0.05$) and there is a significantly ($p<0.01$) negative trend, with the RR estimates lower, and about 1.00, in those studies that had adjusted for three or more variables. In Table C55 (current asthma), the heterogeneity is near significant ($0.05<p<0.1$), with evidence of an increase only seen in those studies that had adjusted for 10 or more variables, studies which all had a relatively large weight (AGABI1, AGABI2, SHOHAT). While there is some

heterogeneity for the analysis of *in utero* exposure (Table E1), no trend is evident. Overall, the results in Table 9.22 do not show any consistent tendency for RR estimates to increase or decrease with increasing number of confounding variables adjusted for.

The general impression that there is no marked effect of adjustment for confounding variables is emphasized by the results of analyses using methods C and D. In the nine main analysis tables (those considered in Table 9.22), there is little consistent tendency for adjustment for any specific confounding variable to have a significant effect on the RR. Occasional significant findings are seen, mainly in those tables where a specific study (or studies) has a large weight and an unusual result, but there seems to be no pattern. In any case, such comparisons are difficult to interpret as RRs which adjust for a specific variable tend also to adjust for more other variables than do RRs which do not adjust for the specific variable.

So far we have demonstrated an association of asthma with exposure that is consistent, dose-related and cannot readily be explained by any of the sources of bias and confounding commonly present in epidemiological studies. Though limitations of the studies preclude a definitive judgement, especially in view of the weakness of the association, the findings seem consistent with some aspect of exposure to tobacco smoke constituents causing an increased risk of asthma. However there are still two key questions that need to be answered. Firstly, is the effect due to postnatal ETS exposure or to exposure *in utero*, or both? Second, does the effect relate to induction or exacerbation of asthma?

Table 9.22. Comparison of relative risks according to number of adjustment variables – children

Table[1]	Numbers of adjustment variables						Numbers of adjustment variables						Heterogeneity		Trend
	0	1	2	3-5	6-9	10+	0	1	2	3-5	6-9	10+	Chisq[3]	p[4]	p[4,5]
	Number of estimates						RRs[2]								
C1	53	14	6	14	18	5	1.16	1.19	1.38	1.14	1.32	1.15	22.49	***	+
C3	33	3	6	12	22	11	1.17	1.08	1.16	1.25	1.17	1.17	1.21	N.S.	N.S.
C5	34	11	3	10	12	2	1.26	1.32	1.37	1.27	1.30	1.28	2.14	N.S.	N.S.
C7	21	3	0	9	7	5	1.24	1.09		1.28	1.20	1.17	1.70	N.S.	N.S.
C45	19	8	4	7	9	2	1.28	1.20	1.37	1.46	1.30	1.34	4.57	N.S.	N.S.
C47	11	4	0	5	4	5	1.32	1.20		1.59	1.20	1.16	7.90	(*)	(-)
C53	21	4	2	3	4	1	1.21	1.16	1.33	0.91	1.00	0.95	14.89	*	--
C55	10	3	0	4	4	3	1.04	1.01		0.83	0.88	1.12	8.99	(*)	N.S.
E1	9	2	1	7	8	5	1.27	0.96	3.30	1.51	1.23	1.23	12.27	*	N.S.

[1] See Table 9.21 for asthma outcome and exposure source corresponding to the Table number. This analysis was not carried out for amount of exposure, Tables D1, D2.

[2] RRs shown are fixed effects estimates.

[3] Chisquared on five degrees of freedom (or four in the case of Tables C7, C47 and C55).

[4] *** p<0.001, ** p<0.01, * p<0.05, (*) p<0.1, N.S. p>0.1.

[5] Based on additional analysis (full details not shown) using trend coefficients of 0, 1, 2, 4, 8 and 12.

9.4.10. Smoking by the Father

The evidence for an association between smoking by the father and risk of asthma is relatively weak. For analyses based on RRs for smoking by the father regardless of the mother (selecting RRs for smoking by the father only when the former RRs are not available), a significant increase of 1.18 (1.13-1.22, n=35) is seen for lifetime asthma from Table C53, but a non-significant increase of 1.04 (0.97-1.10, n=24) is seen for current asthma from Table C55. As noted in §9.3.2 *Other definitions of exposure source*, the estimate for lifetime asthma is based on heterogeneous ($p<0.001$) data, though the random effect estimate of 1.16 (1.09-1.25) is still significant.

A problem with the analyses based on smoking by the father regardless of the mother is that any association seen may partly reflect smoking by the mother, since the smoking habits of husbands and wives are highly correlated (Lee, 1992). In this context it should be noted that the detailed analyses showed that the association is only evident in RRs which were adjusted for no or very few potential confounding variables, and that no real evidence of an association is seen for those RRs that are adjusted for sex, age, other sources of ETS exposure or other factors.

For the analyses based on smoking by the father only, no clear increase in risk is seen, with meta-analysis estimates of 1.11 (0.96-1.29) for lifetime asthma from Table C57 and 1.14 (1.00-1.31) for current asthma from Table C59. These meta-analyses are based on relatively few individual RR estimates, six for lifetime asthma, none of which are statistically significant, and six for current asthma, one of which is significant – the estimate of 1.26 (1.01-1.58) for AGABI1. As shown in Table 9.13, comparison of RRs for smoking by the mother only and for smoking by the father only within studies with both results available shows that the association is generally stronger with maternal than with paternal smoking.

Note that there is only one RR estimate for smoking only by household members other than the parents, the estimate of 1.00 (0.60-1.90) for current asthma for GILLIL which is not significant.

Whereas Tables C57-C60 relate to smoking by the father only, Tables C65-C68 relate to smoking by any household member in the absence of smoking by the mother. For current asthma, the meta-analysis estimates in Tables C67 and C68 are in fact identical to those in Tables C59 and C60, as there are no relevant additional RR estimates. For lifetime asthma, Table C65 has, compared to Table C57, four additional estimates. One of these is significant – that of 2.41 (1.20-4.87) for KERSHA – and the meta-analysis estimate becomes marginally significant, at 1.14 (1.01-1.29).

It should also be noted that, in many of the analyses relating to exposure from sources other than the mother (Tables C57-C68), there are additional studies with incomplete data that could not be included in the meta-analyses, and that none of them reported a significant association with lifetime or current asthma.

Also relevant is the lack of association of any indices of in-life exposure with risk of asthma in studies in Far Eastern countries, where smoking by women tends to be rarer than in Western populations.

Overall, these data provide no clear evidence that smoking by the father, or indeed by household members other than the mother, is associated with an increased risk of asthma. However, though an effect of paternal smoking cannot be inferred with any confidence, the possibility that one exists cannot be excluded. In this context, it is important to note the

relatively small number of studies with relevant data, and the rather lower ETS exposure of the child (as judged by cotinine levels) associated with paternal than maternal smoking (Lee, 1999b).

9.4.11. Discontinued Exposure

As discussed at the end of §9.3.2, some studies have related asthma to discontinued exposure, investigating whether previous but not current exposure is linked to an increased risk. For lifetime asthma, seven RRs give a combined estimate of 1.20 (1.11-1.30). However, the significance is heavily dependent upon the RR (1.22, 1.12-1.33) for a single large study (MCKEEV) and two of the RR estimates are less than 1.00. For current asthma, though one study (AGABI1) shows a significant increase (1.27, 1.06-1.52), the eight RRs taken together show no association, with the combined estimate 1.02 (0.94-1.12). The RRs for discontinued exposure tend to be somewhat lower than those seen for current exposure in the same studies. For lifetime asthma, one can compare meta-analysis estimates of 1.34 (1.26-1.42) for current exposure and 1.20 (1.11-1.30) for discontinued exposure, while for current asthma one can compare estimates of 1.17 (1.08-1.27) for current exposure and 1.04 (0.95-1.15) for discontinued exposure based on those studies providing estimates for both exposures.

If ETS induces asthma, one might expect to see an increased risk of lifetime asthma and no increased risk of current asthma in the children of smokers who quit smoking. If, on the other hand, the association of asthma with parental smoking is due only to an effect of maternal smoking in pregnancy, quitting smoking should not eliminate the risk. Although, superficially, the results for discontinued exposure might seem consistent with the former hypothesis, there are a number of reasons why an effect of ETS cannot reliably be inferred. These include the relatively small number of studies, and the dominance of individual studies, as well as the fact that the exposure which was discontinued comes from a variety of sources – for lifetime asthma, two of the RRs relate to the mother, three to any parent and two to any household member, while for current asthma, five relate to the mother, one to the father and two to any household member. Another problem is that all but one of the estimates for mother, father or any parent relate to being an ex-smoker, so that smoking may have been discontinued before the child was born (or conceived). Also, smokers who quit may tend to have smoked less when they were smoking than did smokers who continued to smoke. Clearly, more data are needed on discontinued exposure.

9.4.12. Smoking in Pregnancy

The data on smoking by the father and on discontinued exposure summarized in the previous two sections offer somewhat indirect evidence relating to the role of ETS in the causation of asthma. Of more direct relevance are the data from studies that have presented separate RRs for in-life exposure only, *in utero* exposure only, and for both in-life and *in utero* exposure. The relevant data are discussed in some detail in §9.3.6. These data, though somewhat limited, show no significant association of in-life only exposure with risk of asthma, but a significant increase associated with *in utero* only exposure or with both exposures. The RRs for lifetime/current asthma associated with maternal smoking are 1.08

(0.99-1.18) for in-life only exposure, 1.41 (1.14-1.75) for *in utero* only exposure and 1.33 (1.21-1.46) for both exposures. These results are consistent with maternal smoking in pregnancy, but not ETS, causing asthma, though they do not exclude the possibility of a weaker effect of ETS exposure.

§9.3.6 also includes presentation of rather limited data relating to the effect that adjustment for *in utero* exposure had on RRs for in-life exposure and the effect that adjustment for in-life exposure had on RRs for *in utero* exposure. These comparisons tend not to be very informative, partly because they are based on few studies, partly because quite a number of the results are reported simply as not significant, and partly because comparison is typically between unadjusted RRs and RRs adjusted for a whole range of potential confounding variables in addition to the variable of interest.

The conclusion that any relationship with asthma is predominantly with exposure during gestation and not with ETS exposure postnatally is consistent with the results of four more recent publications that provided information on the separate associations. These appeared in 2005/06 and were therefore not considered in our analyses.

The first publication describes a nested case-control study in California involving 338 children with asthma diagnosed in the first five years of life and 570 control subjects. Thus the subjects are a subset of those already considered as study GILLIL. Li et al. (2005) reported that children of mothers who continued smoking throughout pregnancy had an increased RR (1.6, 95% CI 1.0-2.6) compared to children whose mothers never smoked. In contrast postnatal ETS exposure, as indexed by having smokers in the household, was only weakly associated with asthma occurrence (1.2, 0.8-1.7), with the association further reduced after adjustment for *in utero* exposure to maternal smoking (0.9, 0.6-1.4).

The second publication (Gilliland et al., 2006) provides further analysis of the prospective part of the California study already considered as MCCON1, with follow-up extended to high school graduation. Although the main focus is on the role in the onset of asthma of active smoking, some analyses are presented on the role of maternal smoking in pregnancy and postnatally. Excluding the 7% of children who smoked regularly (7+ cigarettes in the last week), no significant effect was seen, with RRs 1.1 (0.6-2.0) for exposure *in utero* only, and 0.7 (0.4-1.2) for exposure both *in utero* and postnatally, compared with children with no maternal exposure. No information was given for children exposed to maternal smoking postnatally but not *in utero*.

The third publication describes a cohort study of 2031 boys and 1884 girls born in Australia in 1981-84. Alati et al. (2006) related asthma at age 14 to maternal smoking habits measured early and late in pregnancy and at age 6 months. There was no association between maternal smoking and asthma symptoms in boys after adjustment for multiple potential confounding variables. Nor was past but not current asthma related to maternal smoking in girls. However, in girls, current asthma (last 6 months) was significantly increased where the mother had smoked heavily (20+ cigs/day) during pregnancy (1.96, 1.25-3.08) but was not significantly increased where the mother had smoked heavily after, but not during, pregnancy (1.20, 0.80-1.81) or where the mother had smoked, but never heavily, at any of the measured times (0.81, 0.60-1.09).

The fourth publication describes a cross-sectional study of 1561 Polish schoolchildren aged 9-11 years. Zlotkowska & Zejda (2005) reported no significant increase in risk of lifetime asthma in children exposed only postnatally (1.1, 95% CI 0.5-2.8) or in children

exposed both *in utero* and postnatally (1.2, 0.4-3.3) as compared to children with no maternal exposure.

9.4.13. Exacerbation or Induction?

While studies that clearly relate to exacerbation have already been considered in chapters 3 to 6, it is clear, for reasons already discussed in §8.4.11, that there are difficulties in interpreting all the results from these studies strictly in terms of induction. As noted, induction relates to the probability of a previously asthma-free child getting the condition for the first time, and an ideal study on induction would involve either a prospective study of children who were asthma-free at the start of the study, with subsequent collection of data on time of asthma onset and changes in ETS exposure, or a case-control or cross-sectional study, in which detailed retrospective information on time of asthma onset and history of ETS exposure was obtained.

As for adults, the data collected rarely conform to this ideal, many of the studies only collecting information on whether the child is currently asthmatic. The lack of data on time of onset of asthma means that one cannot interpret an association of, say, maternal smoking with asthma as indicating a specific effect on either induction or exacerbation. More insight can be gained from studies of whether the child has ever had asthma. Assuming that the child did not have asthma diagnosed at birth, which seems unlikely, the endpoint can be interpreted as induction between birth and age C, the current age of the child.

Even then there is a problem in that many studies collect data relating to ETS exposure at age C rather than between birth and onset of asthma. For induction to be inferred, exposure has to occur before onset. However, if one is willing to accept that the smoking habits of parents (and household members) are likely to remain relatively constant, current smoking habits may be taken to approximate smoking habits before the time of onset of asthma. However, this may not be so if presence of asthma in a child affects the smoking habits of the parents – parents may cut down or give up smoking if they believe that their smoking may exacerbate their child's asthma. However, the data provide little evidence of this. As discussed in §9.3.2, RR estimates for lifetime asthma for both total and parental exposure are virtually unaffected by whether the most recent or the earliest estimate of in-life exposure is used. For example, for parental exposure, Table C13 (recent exposure) gives a meta-analysis estimate of 1.27 (1.23-1.31), while Table C21 (earliest exposure) gives an estimate of 1.27 (1.23-1.31). Although, of the 72 estimates included in each of these meta-analyses, 63 are the same (as the study only provides one relevant estimate), the nine pairs that are based on different exposure timing show no consistent or marked difference, as shown in Table 9.23.

Inspection of this table reveals a further difficulty in that in five of the nine studies, the index of earliest smoking used was "ever," so that, as they were all of case-control or cross-sectional design, the smoking by the parent may have occurred before the birth of the child. For only three studies (KUEHR, SHERMA and SOYSET) did earliest smoking relate to a period in the child's life that was very likely to be before asthma onset.

Table 9.23. Effect of timing of parental smoking on relative risks for lifetime asthma – children

	Study	Recent smoking (Table C13)		Earliest smoking (Table C21)	
Study	type[1]	When	RR (95% CI)	When	RR (95% CI)
BUTZ	CC	Current	1.12 (0.51-2.46)	Ever	1.24 (0.72-2.14)
CHEN2	CS	Current	1.72 (0.95-3.10)	Ever	1.67 (1.01-2.77)
EHRLI2	CC	Current	1.90 (1.10-3.60)	Ever	2.00 (1.10-3.80)
KUEHR	CS	Current	0.77 (0.53-1.12)	Age <1 year	0.68 (0.44-1.06)
KUHR	CS	Current	1.90 (1.01-3.59)	In life	2.01 (0.88-4.61)
MCKEEV	Pr	Current	1.31 (1.23-1.40)	Ever	1.31 (1.24-1.39)
SHERMA	Pr	Ever	1.18 (0.76-1.83)	Ever 1 year ago	1.09 (0.68-1.74)
SOYSET	CS	Current	1.17 (0.66-2.07)	Age <1 year	1.24 (0.70-2.20)
VERHOE	CC	Current	0.74 (0.48-1.14)	Ever	0.78 (0.49-1.25)

[1] CC = case-control; CS = cross-sectional; Pr = prospective; see also §9.1.4 "Design."

Of the 227 studies considered in this review, few actually reported results which appeared to relate onset of asthma to smoking by parents (or other household members) occurring in the preceding lifetime of the child. Only seven studies, four prospective and three case-control studies, clearly qualify in this respect. The three case-control studies limited attention to cases with first occurrence of asthma, INFANT considering exposure since birth, and AZIZ1 and WILLE1 current exposure. Of the prospective studies, PONSON followed up children from shortly after birth and related postnatal exposure at baseline to subsequent onset of asthma. MARTIN and MCCON1 followed up older children, but restricted attention to those without a history of asthma at baseline, linking exposure at baseline to subsequent onset of asthma. SHERMA had a baseline interview in 1975, when the children were aged 5-9, and then subsequent interviews from 1978-1988, covering both exposure and presence of asthma. Formal onset analysis methods were used, so that only exposure of asthma-free children was considered at any point.

There are three other prospective studies which might also be considered to qualify, but not so clearly. Two of these studies, RONMA3 and WICKMA, used exposure indices, respectively *"mother's past or present smoking,"* and *"during pregnancy and/or at the time of enrolment [age 2 months],"* which do not distinguish *in utero* and in-life exposure. ULRIK followed up children excluding only those with asthmatic symptoms at baseline (rather than all those with a history of asthma), thus possibly including some with pre-existing asthma.

It is interesting to note that there were some other prospective studies where data seemed to have been collected that would have allowed relevant analysis, but where either the appropriate outcome (HALONE, JAAKKO, PETERS) or the appropriate exposure variable (LEEDER, TAYLOR) was not analysed, where the analysis was not clearly described (BURR, BERGMA, MILLER), or where the description of the exposure variable was too unclear to be confident that the smoking preceded the asthma (FERGUS, MCKEEV, ODDY, SIGURS, ZEIGER).

Meta-analysis of all the relevant data from the studies described in the previous three paragraphs gave an estimate of 1.27 (1.21-1.34, n=17) for total exposure (Table C29), with a further three studies providing only incomplete information, all non-significant. Additional analysis (details not given) showed that if attention was restricted only to those studies that

clearly related asthma onset to preceding in-life exposure, the estimate becomes 1.17 (1.03-1.34, n=8), the change being largely due to the exclusion of study MCKEEV which accounted for 69% of the weight in the original analysis. For parental exposure, the equivalent estimates are virtually identical. Even though the association of preceding in-life exposure with asthma onset is statistically significant, it should be noted that none of the six studies that contributed to this estimate (INFANT, MARTIN, MCCON1, PONSON, SHERMA, WILLE1) separated effects of *in utero* and in-life exposure, while the other study where exposure clearly preceded asthma onset (AZIZI) found no mothers who smoked and no association with paternal smoking. One therefore cannot exclude the possibility that any true relationship was actually with *in utero* exposure.

There are also a number of cross-sectional studies which related exposure when the child was very young to the presence of asthma some years later. Thus HABY considered exposure before age six months, KUEHR and SOYSET exposure before age one year, and FORSB1, FORSB2, FORSB3, STERN2, TIMONE and WILLE2 considered exposure before age two years, but here one cannot strictly rule out that the asthma occurred before the exposure. STRACH considered exposure *"around time of child's birth"* which does not distinguish *in utero* and in-life exposure.

The above discussion shows clearly that the number of studies which allow inferences regarding induction of asthma to be drawn is quite limited. Though there is some evidence of an association of induction of asthma with preceding exposure, it is not demonstrated whether this results from an effect of ETS or of *in utero* exposure.

9.5. Summary and Conclusions

9.5.1. Methods Used to Collect and Analyse the Data and Scope of the Information Obtained

Based on papers published up to the end of 2004, epidemiological studies of prevalent or incident asthma in children have been identified. As for adults only studies where the endpoint was "asthma" were included, with studies of e.g. "wheezing bronchitis" excluded. Also, as for adults, two linked databases were set up, one containing details of the characteristics of each study, with the other containing RR data relating to certain aspects of ETS exposure.

After examining over 1100 papers, 217 principal studies were identified (143 cross-sectional, 42 case-control and 32 prospective) together with 10 subsidiary studies with data which overlap with those of principal studies, their data only being used in meta-analyses where equivalent results are not available from the principal studies. Defined methods were used for entry and checking of data, and derivation of RRs.

The 217 principal studies were conducted in 44 countries in all continents except Antarctica, most commonly in the US (39 studies), UK (24), Canada (13), Germany (13) and Sweden (11). 21 started in the 1970s or earlier, with 53 starting in the 1980s and 107 in the 1990s. All but two studies considered children of both sexes. The lower age limit of children in the study was below 5 years for 75 studies, in the range 5-9 years for 109 studies, and 10 or more years for 32. About one third of the studies used the standard questionnaires ISAAC,

ATS or WHO. Results for lifetime or incident asthma were available from 134 principal studies, and for current asthma from 105. The distribution of the number of asthma cases was very skew, ranging from 6 to 5842 (median 168.5) for lifetime or incident asthma and from 8 to 20637 (median 137) for current asthma. 75% of all studies and 69% of studies including children aged 10 and above did not mention smoking by the child. 38% of the studies did not adjust for any variables at all in analysis. About half the studies adjusted for four or more potential confounders, with 13% adjusting for 10 or more.

Of the total of 1335 RRs available, 1318 relate to the principal studies. The number of relevant RRs per principal study varies widely, from only one in 64 studies, to over 10 in 29, the largest being a study with 81 RRs entered. 1245 RRs are for sexes combined, and 1136 for the full age range of the study. 595 relate to prevalent lifetime asthma and 644 to current asthma, with only 96 relating to asthma onset. 824 of the RRs relate to parental smoking and 359 to household smoking, with 46 to biochemical exposure, 20 to total exposure, 15 to parental ETS exposure and 71 to combinations of *in utero* and in-life exposure. 486 RRs relate to current ETS exposure, 341 to exposure with the timing unspecified, 132 to *in utero* exposure (regardless of in-life exposure) and 122 to exposure during the child's lifetime generally. 283 RRs from 42 studies are dose-response data. 643 RRs are adjusted for at least one variable. 121 have no RR value and only a statement of significance or non-significance, and a further 55 lack a CI. 692 RRs are either as given originally or were calculated directly from numbers in the relevant 2 × 2 table (or tables). The rest involved more complex calculations.

Table 9.24. Summary of meta-analyses for in-life exposure – children

Exposure	Lifetime asthma		Current asthma	
	n	RR (95% CI)[1]	n	RR (95%CI)[1]
Total[2]	110	1.23 (1.17-1.29)	87	1.23 (1.17-1.29)
Parent[3]	72	1.27 (1.21-1.33)	45	1.21 (1.11-1.33)
Both parents	9	1.44 (1.22-1.70)	7	1.69 (1.25-2.27)
Mother/mother only[4]	49	1.31 (1.24-1.40)	29	1.25 (1.12-1.40)
Mother only	4	1.16 (0.80-1.67)	5	1.38 (1.03-1.85)
Father/father only[5]	35	1.16 (1.09-1.25)	24	1.02 (0.94-1.10)
Father only	6	1.11 (0.96-1.29)	6	1.15 (0.98-1.34)
Household exposure other than parents	4	1.41 (1.14-1.73)	6	1.49 (1.30-1.71)
Household exposure but not mother[6]	10	1.14 (1.00-1.30)	6	1.15 (0.98-1.34)

[1] Random effects estimates using RRs adjusted for covariates where adjusted data are available.
[2] Preferring, in order, RR estimates for biochemical, total, household and parental exposure.
[3] Preferring RR estimates for mother to those for father if estimates for any parent not available.
[4] Preferring RR estimates for mother regardless of father to those for mother only.
[5] Preferring RR estimates for father regardless of mother to those for father only.
[6] Preferring RR estimates for father only where alternatives are available.

9.5.2. Results

Results are presented of a series of meta-analyses of the database aimed at giving insight into how the RR of asthma varies by the source, timing and amount of the exposure to parental smoking/ETS, the definition of the unexposed group, the definition of the asthma outcome, the sex and age of the child, the location, timing, size and type of study, the source of the information on exposure and diagnosis, and the extent of adjustment for confounding variables.

The main conclusions reached from the analyses are as follows:

There is an association between in-life exposure to parental smoking and either lifetime or current asthma. As illustrated in Table 9.24, which summarizes RRs and 95% CIs from random effects meta-analyses, the association is stronger in relation to maternal than paternal smoking and is not statistically significant where the mother does not smoke (exposure = father only, or household exposure but not mother).

There is evidence of a dose-response relationship. For those studies which provide RRs by extent of exposure, typically in terms of number of cigarettes per day or number of persons in the household who smoke, estimates (relative to no exposure) are higher for the highest exposure category considered than for the lowest. For lifetime asthma, random effects estimates based on 19 pairs of RRs were 1.39 (1.16-1.68) for high exposure and 1.07 (0.93-1.22) for low exposure. For current asthma, estimates are 1.40 (1.22-1.60) for high exposure and 1.08 (0.97-1.21) for low exposure based on 21 pairs.

Although many of the meta-analyses conducted show statistically significant heterogeneity between the individual RR estimates, associations seen for total, parental and maternal exposure are generally consistently seen in subsets of the data defined by a wide range of factors. A possible exception is that studies conducted in the Far East do not show evidence of an association. There is evidence in some of the analyses, but not all, that associations may be weaker in older than younger children, in studies where the child was the respondent for questions on either ETS exposure or diagnosis of asthma, in studies where steps had been taken to exclude children who smoked, and in cross-sectional and prospective studies rather than case-control studies. However, the prevailing impression is of a highly consistent association.

Analysis of the RRs included in the meta-analyses do not show any particular indication of publication bias. However, there are quite a large number of studies that could have provided data suitable to be included in meta-analyses, but which had not done so, and a suggestion that significant associations in these incompletely reported studies are less frequently seen than in the studies included in the meta-analyses. These findings do not, however, suggest that publication bias is a major issue.

There is no clear evidence of confounding by a variety of non-smoking lifestyle factors, although a number of different approaches were used to investigate this. There also seems no reason to believe that the association had arisen because of misclassification of exposure or diagnosis, or due to unreported smoking by the child.

There is a highly significant ($p<0.001$) association of asthma with maternal smoking in pregnancy, with a random effects estimate of 1.31 (1.19-1.45) based on 32 individual RRs for lifetime or current asthma. Dose-response data are limited, but quite consistently show a significant increase at high dose but little or no increase at low dose.

Eight studies presented RRs separating the individual associations with *in utero* and in-life exposure. There is a significant increase in risk associated with *in utero* only exposure (1.53, 1.05-2.23, n = 7) and with combined *in utero* and in-life exposure (1.32, 1.18-1.49, n = 9) but not with in-life only exposure (1.08, 0.99-1.18, n = 7), based on results with a preference for lifetime over current asthma. Preferring current over lifetime asthma does not affect the conclusion that in-life only exposure is not associated with an increase in risk. Indeed, with the exception of one small study, all RR estimates are very close to 1.00.

Most of the studies do not separate out possible effects on induction and on exacerbation. Only seven studies clearly related onset of asthma to preceding in-life exposure. While the results from these studies showed some association (1.17, 1.03-1.34, n=8), potential confounding by *in utero* exposure could not be excluded.

9.5.3. Other Reviews

Early Reviews

There have been a large number of review papers that have considered the question of whether ETS exposure can induce asthma in children, many only briefly in a more wide ranging review of effects of ETS or risk factors for asthma. Early major reviews of possible health effects of ETS either did not discuss at all the possibility that ETS exposure might induce asthma (Committee on Passive Smoking, 1986) or noted that "*further investigation is needed to determine whether*" it can do so (US Surgeon General, 1986).

During the early 1990s, as the literature available increased, more comprehensive reviews started to appear. Thus in 1990 a report of a working group on passive smoking (Spitzer et al., 1990) concluded that *"the evidence strongly supports a relationship between exposure to environmental tobacco smoke and asthma among children,"* but did not attempt to discriminate between effects on induction and exacerbation or discuss the potential role of smoking in pregnancy. The next year a review of ETS (Samet et al., 1991) considered that the *"evidence for association of involuntary smoking with childhood asthma is conflicting,"* noting that though *"exposure to ETS might cause asthma as a long-term consequence of the increased occurrence of lower respiratory infection to early childhood or through other mechanisms"* it *"has not been established as a cause of asthma."* Difficulties in interpretation were also highlighted in a review on respiratory health effects in children (Hood et al., 1992) which concluded that *"Although the association between parental smoking and increased incidence of respiratory symptoms and certain diseases in young children has been observed repeatedly, the mechanism of this association remains unexplained. Among the possibilities that should be considered are an ETS effect, pregnancy and/or lactation-related effects, and SES-related confounders."* The potential importance of smoking in pregnancy was also highlighted in another review in the same year (Evans & Golding, 1992) and in a review the next year (Ehrlich et al., 1993) which found that maternal smoking was generally related to asthma in children, but paternal smoking was not and noted that *"This maternal predominance may reflect in utero influences, the child's inhalational exposure to ETS from maternal sources, or both"* and that *"it is difficult to separate these influences epidemiologically."*

The reviews cited above were generally of a descriptive nature and not necessarily complete, with none involving meta-analysis. This changed when major detailed overviews

were carried out in the UK by Cook and Strachan (Cook & Strachan, 1997; Strachan & Cook, 1997; Strachan & Cook, 1998) and in the US by the California EPA (National Cancer Institute, 1999; California Environmental Protection Agency, 2005). Since other reviews (e.g. Jaakkola, 2000; Institute of Medicine (US), 2000) have relied heavily on these reviews, and since their conclusions are considerably different, we concentrate below on these major reviews and do not comment on other, often much briefer, reviews that have appeared in recent years (e.g. Esamai, 1998; Chidekel, 2000; Gold, 2000; Gergen, 2001; McQuaid et al., 2003; Walker et al., 2003; King et al., 2004).

Reviews by Cook and Strachan

The first review paper by Strachan and Cook concerning parental smoking and health effects in children is entitled "*Parental smoking and lower respiratory illness in infancy and early childhood"* (Strachan & Cook, 1997). Although this did not specifically look at asthma, part of the review considered 10 community studies of wheezing illness. Five of these provided data on risk relating to either parent smoking, for which a combined RR of 1.54 (1.30-1.81) was reported. For mother smoking the estimate was 1.98 (1.71-2.30), based on seven studies, and for father only smoking it was 1.19 (0.92-1.53), based on three studies. The main conclusion of the paper was:

> "The relationship between parental smoking and acute lower respiratory illness in infancy is very likely to be causal. Although it is impossible to distinguish the independent contributions of prenatal and postnatal maternal smoking, the increased risk associated with smoking by other household members suggests that exposure to environmental tobacco smoke after birth is a cause of acute chest illness in young children."

However, it should be noted that this was based to a considerable extent on analyses for endpoints alternative to wheezing illness. Elsewhere in the paper the authors state that *"maternal smoking appears to be relatively more important, and paternal smoking perhaps less important in studies which have ascertained wheezing illness specifically."*

The same year these two authors published a further paper (Cook & Strachan, 1997) entitled "*Parental smoking and prevalence of respiratory symptoms and asthma in school age children."* This review considered asthma, wheeze, cough, phlegm and breathlessness and was restricted to population surveys (i.e. cross-sectional studies). They identified 25 studies of asthma, with results reported for five indices of parental smoking. Meta-analysis results were as follows: either parent smokes 1.21 (1.10-1.34, n=21), one parent smokes 1.04 (0.78-1.38, n=6), both parents smoke 1.50 (1.29-1.73, n=8), mother only smokes 1.36 (1.20-1.55, n=11) and father only smokes 1.07 (0.92-1.24, n=9).

They concluded that:

> "The relationship between parental smoking and respiratory symptoms seems very likely to be causal given statistical significance, robustness to adjustment for confounding factors, consistency of the findings in different countries, and the evidence of dose response. The raised risk in households where the father, but not the mother, smoked argues for a postnatal effect."

There are a number of similarities about their analyses and ours. Thus, they reported a similar magnitude of association, statistical significance but some heterogeneity, consistency

across countries, a dose-response relationship and lack of effect of confounder adjustment. They found that *"those studies reporting the highest odds ratio were more likely to be early publications, to be small, and not to adjust for confounders,"* suggesting some publication bias. We did not find evidence of publication bias in our analyses based on studies of all designs, but we agree that publication bias is not likely to be an important biasing factor. They also noted that the evidence relating to parental smoking in the past is unclear because *"so few data have been published and ex-smokers are likely to have been lighter smokers."*

It is important to note, however, that their final conclusion that *"the raised risk in households where the father, but not the mother, smoked argues for a postnatal effect"* appears to be largely due to their analyses of data for wheeze and cough, where the RRs for father only smoking were higher and statistically significant – 1.14 (1.06-1.23, n=10 for wheeze) and 1.21 (1.09-1.34, n=9 for cough).

It is interesting that, whereas Cook and Strachan reported nine RR estimates for father only smoking based on cross-sectional studies alone, our analyses based on all study designs include only six such estimates for lifetime asthma and four for current asthma. An investigation to see whether we might have missed relevant data revealed that, of the nine estimates for father only smoking reported by Cook and Strachan, five (for studies CHEN2, GOREN2, SOTOQU, SOYSET and STERN1) have a footnote in their Table 2 indicating that the data are actually for *"father currently smokes versus not"* and are thus not actually for father only smoking at all. Furthermore, for study GOREN1, the estimate cited is actually for household member other than mother smokes and not for father only smokes, and for study KAY, though we both include estimates, they cited an estimate unadjusted for covariates (1.3, 0.86-1.97), whereas we use a somewhat lower adjusted estimate (1.25, 0.81-1.92). They included an estimate from study BURCHF of 0.76 (0.56-1.04) for which the source is unclear – we only have non-significant estimates of 0.84 for boys and 0.65 for girls without any CI and cannot see how Cook and Strachan derived their CI estimates so as to allow inclusion of the study in the meta-analyses. Indeed, our estimates only agree for one study (FORAST), and we also have data from three further cross-sectional studies (DOLD, GILLIL and VENNER).

Our conclusion from this investigation is that Cook and Strachan's estimate of 1.07 (0.92-1.24) for father only smoking is not actually a true estimate for father only smoking at all, and emphasizes the importance of deriving meta-analysis estimates for consistently defined indices of exposure (and disease). The same conclusions can be drawn from a similar investigation of their data for mother only smoking, for which six of the eleven estimates included in their meta-analyses have footnotes indicating that they actually relate to *"mother currently smokes versus not"* and one to *"mother smoked in pregnancy and infancy versus not."*

In 1998 the same two authors published a paper entitled *"Parental smoking and childhood asthma: longitudinal and case-control studies"* (Strachan & Cook, 1998). Four main groups of studies were considered: incidence studies, natural history studies, case-control studies and case series. The natural history studies and the case series relate to asthma exacerbation (or prognosis) and are not considered in detail here. Their definition of asthma included some studies which we would have excluded as being based on wheezing. There were two relevant RRs reported for the incidence (prospective) studies, maternal smoking for occurrence in the first 5-7 years of life 1.31 (1.22-1.41, n=4) and maternal smoking for occurrence later in childhood 1.13 (1.04-1.22, n=4). Based on the case-control studies they

reported meta-analysis estimates of 1.37 (1.15-1.64, n=14) for parental smoking, 1.59 (1.27-1.99, n=8) for maternal smoking and 0.94 (0.78-1.12, n=8) for paternal smoking. However, they do not report results for mother only or father only smoking. The authors concluded that:

> "The excess incidence of wheezing in smoking households appears to be largely non-atopic "wheezy bronchitis" with a relatively benign prognosis, but among children with established asthma, parental smoking is associated with more severe disease. This apparent paradox may be reconciled if environmental tobacco smoke is considered a co-factor provoking wheezing attacks, rather than a cause of the underlying asthmatic tendency."

It is interesting that this conclusion, based on the results of all the studies, including those on asthma exacerbation, supports the view that ETS does not induce asthma. However, it is clear from the paper that the mechanism they propose, considering ETS as *"a co-factor operating with intercurrent infections as a trigger of wheezing attacks, rather than as a factor initiating or inducing the asthmatic state"* is more a proposal than a definitive conclusion. It is interesting that they note in the paper that *"in case-control studies maternal smoking appears to be the dominant influence, with little effect from smoking by the father"* and that the *"weak association between the incidence of asthma and paternal smoking"* seen in *"most longitudinal studies" "could be partially due to confounding by maternal smoking."*

Comparison of our findings with those of Strachan and Cook is complicated by their splitting their analyses into three papers, their not using consistent exposure indices in each paper, their consideration of endpoints other than asthma and tending to generalize from these results to asthma, and their including results for wheezing in some analyses. Nevertheless their results show considerable similarity to ours. In this context it is interesting particularly to note that none of their meta-analyses for father smoking show a significant increase in risk. Even when combined, the RR estimates from the three papers, (Cook & Strachan, 1997; Strachan & Cook, 1997; Strachan & Cook, 1998) of 1.19 (0.92-1.53) and 1.07 (0.92-1.24) for father only smoking, and 0.94 (0.78-1.12) for father smoking give an overall estimate of 1.04 (0.94-1.16), which is not significant. This agrees with our conclusions.

Their papers pay little attention to distinguishing effects of ETS and of maternal smoking in pregnancy, tending to assume associations seen with maternal smoking are due to ETS. Even then, however, they are much more certain there is an exacerbating rather than an inducing effect.

The California EPA Reports

In their review of the *"Health Effects of Exposure to Environmental Tobacco Smoke"* the California EPA (National Cancer Institute, 1999) devoted separate sections to asthma exacerbation and to asthma induction. They concluded that *"there is consistent and compelling evidence that ETS is a risk factor for induction of new cases of asthma."*

They identified 37 studies that satisfied four criteria:

- the endpoint must represent the development of asthma in persons up to 18 years of age. Studies that examined outcomes of "wheezy bronchitis" or "constant wheeze/whistling in the chest" were also included and analysed separately and jointly with those studies which examined only physician-diagnosed asthma;
- postnatal household exposure must be studied;

- relative risks or odds ratios (and their SEs) must be reported or be calculable from data available; and
- studies must be independent.

RRs and 95% CIs were presented graphically for 27 studies that used clinically recognized asthma as the outcome and for 17 studies that used "wheezing bronchitis" or "chronic wheezing/whistling in the chest" as an outcome. No indication was given in the figures or text as to which exposure index was selected.

The California EPA reported a combined estimate of 1.44 (1.27-1.64) for clinically recognized asthma and 1.47 (1.34-1.61) for the alternative outcome. They noted some heterogeneity but elevated RRs in all subgroups investigated. The pooled RR was noted to be 1.60 (1.29-1.99) for maternal smoking and 1.34 (1.11-1.61) for household smoking only. The analyses reported include no formal assessment of dose-response or any estimation of the association with paternal smoking.

They appear to have based their conclusion of a causal effect of ETS exposure on asthma induction on a number of factors:

- *a "strong and consistent association between exposure to ETS and development of childhood asthma"* – though they do not define strong and RRs of about 1.5 are not generally considered to be strong;
- a dose-response – noting that *"there appears to be a simple biological gradient of effect (or dose-response) in studies that collected data on levels of smoking, where effects were detectable only when the mother smoked 10 or more cigarettes per day (e.g. Martinez et al. 1992)"*;
- higher RR estimates in studies using *"more precise measures of exposure"* – basing this conclusion on a very limited number of studies that used cotinine, some of which related to their alternative outcome rather than to asthma;
- higher RR estimates in studies involving pre-school children;
- the association with ETS being generally independent of confounder adjustment, with those studies which *"controlled for three or more potential confounders and effect modifiers"* tending *"to have **greater** estimates of RR of asthma than those studies that adjusted for fewer than three covariates,"* [our emphasis] a conclusion that we certainly did not find;
- effects seen in relation to paternal smoking – citing results from various studies in China by Chen (Chen & Li, 1986; Chen et al., 1986; Chen et al., 1988; Chen, 1989), only one of which actually concerns asthma at all; and
- biological plausibility – claiming that:

> "1) ETS exposure predisposes young children to an increased risk of repeated respiratory infection, a recognized risk factor for the development of asthma; 2) ETS causes airway hyperresponsiveness; 3) ETS may increase the risk of childhood atopy and of increased circulating allergy-related antibodies (IgE), enhancing the probability of allergic asthma; and 4) cigarette smoke causes airway inflammation in active smokers (Niewoehner et al., 1974) and may have similar (but lower-level) effects in people exposed to sidestream smoke."

Study of this report reveals a number of severe limitations. These include drawing conclusions on dose-response and effects of paternal smoking without carrying out any proper overall assessment of the evidence, failure to look at effects of confounder adjustment within-study, failure properly to separate possible effects of *in utero* and in-life exposure, and failure adequately to address the difficulties in distinguishing effects on asthma induction and asthma exacerbation from the data that they have considered.

The meta-analysis estimate of 1.44 (1.27-1.64) that they reported for clinically recognized asthma is markedly higher than those that we found for total exposure; 1.23 (1.17-1.29) for lifetime asthma and 1.20 (1.13-1.27) for current asthma, and it is therefore important to try to see why this difference arose. An investigation of the issue led to the following observations:

- the data included in the meta-analysis are presented only graphically, in Figure 6.1 of their report (National Cancer Institute, 1999), which makes it difficult to assess the actual data used;
- neither the text of the report, nor Figure 6.1, makes it clear what exposure index has been used. The second criterion noted above demands that it must be "*postnatal household exposure"* but within that definition there is considerable scope for selection of estimates in some studies;
- nor does the report or the figure define whether the RR concerns lifetime or current asthma;
- nor is any information given concerning whether results cited are adjusted or unadjusted for covariates;
- we have included estimates for all the 27 studies considered in their Figure 6.1, though for some studies we used alternative estimates from other papers;
- Figure 6.1 includes an estimate from one study (Bener et al., 1991) which has a 95% CI that is so narrow that it cannot be seen. We had rejected this paper (§9.1.3) because of various discrepancies and because, from comparison with two other papers (Al Frayh et al., 1989; Al Frayh, 1990), which we did use for our estimates, it appeared to relate to wheeze, not asthma. The paper EPA used (Bener et al., 1991) reported results from a logistic regression which, when converted into odds ratios, gave estimates of 1.15 (1.09-1.22) for father smoking and 1.04 (0.99-1.10) for mother smoking, which both implied (see Lee, 1999a) numbers of subjects far in excess of those studied. Clearly, the estimate used by California EPA from this study had a CI that was far too narrow, so that its weighting in the meta-analysis would be much too high;
- in two studies (PALMIE and MURRAY), the source data give separate RRs for atopic and non-atopic children. While these estimates can readily be combined, and we have done so for our estimates, Figure 6.1 selects, for no apparent reason, results for atopic children for MURRAY and results for non-atopic children for PALMIE;
- where the source data give results by level of exposure, we have calculated estimates for combined exposure, but the California EPA have not, apparently using only the RR for high exposure in studies PALMIE, INFANT and DODGE;

- in study BURCHF, where equivalent results for both sexes are available, Figure 6.1 (asthma) appears to present data for boys, while Figure 6.2 (wheeze) appears to present data for girls;
- for study MCCON2, we had included an estimate of 0.56 (0.12-2.56) for lifetime asthma based on results reported in (McConnochie & Roghmann, 1986), having rejected the paper cited in Figure 6.1 (McConnochie & Roghmann, 1989) as lacking detail. Although the later paper presents some data suggesting an association of maternal smoking with wheezing, it presents no RR for asthma consistent with the value of about 2.8 shown in the Figure, and indeed includes a statement *"None of the passive smoking variables predicted asthma at either of the interviews;"* and
- study WEITZ1 was included although exposure was *in utero*, so did not meet the second criterion noted above.

From this investigation, it can be concluded that the meta-analysis is extremely poorly described and presented, and is based on estimates that are not derived on any sort of consistent basis, some of which are clearly inappropriate. Taking into account also the limitations noted above, it is abundantly clear that this rather poor piece of work provides no valid scientific justification for the conclusion of the California EPA that ETS induces asthma in children.

Recently, in their *"Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant"* (California EPA, 2005), the California EPA presented an updated section on asthma induction in children. Mainly, this involves reference back to their earlier report (National Cancer Institute, 1999), and a brief description and summary of the results from studies published up to 2001 not previously considered. The final part of the section on asthma induction notes that an *"analysis based on 29 studies that controlled for the child's history of atopy and personal smoking, and in which all ages were combined gave a pooled OR for new-onset asthma of 1.32 (95% CI 1.24-1.41)."* While it is stated that *"for the purposes of meta-analysis, relative risk estimates were extracted according to preset exclusion/inclusion criteria, and represented various combinations of exposure and outcome definition, subgroup stratification, and levels of exposure,"* no further details are given and the odds ratios combined in the analysis are not presented. It thus becomes impossible to evaluate properly the work that has been conducted or to compare it with our own work.

The updated California EPA report contains a table (6.34) on *"Effect of timing of ETS exposure on risk of asthma induction"* presenting RRs and 95% CI for eight studies that looked at postnatal-only exposure. It was noted that such exposure *"resulted in elevated asthma risk in seven of eight studies, and that risk was statistically significant in three of the studies."* The eight estimates for postnatal only exposure in Table 6.34 can be compared with those for "exposure in life only" shown in our Table 9.17 which, as we noted in §9.3.6, are generally consistent with a lack of association with asthma.

Comparing the estimates from the two sources a number of points can be made:

- Table 6.34 of the updated report gives no detail of the source of the in-life exposure (mother, father, any household member, biochemical) or of the definition of asthma used (lifetime, current), and it is unclear what criteria were used to select the estimates presented;

- it would appear from the text preceding Table 6.34 that the studies selected all controlled for child's smoking and history of atopy. In fact, examination of the source papers indicates that this was often not the situation. Thus, for example, studies AGABI1 and AGABI2 adjusted for parental history of asthma, not the child's;
- our Table 9.18 includes results from three studies (CUNNI1, LOPEZC, TARIQ), all of which showed no association of asthma with in-life only exposure, which were not considered in Table 6.34;
- there appear to be possible typographical errors in Table 6.34, in that two successive RR estimates, 1.08 and 1.24, have the same 95% CI of 0.91-1.61, despite the fact that 1.08 is very far from the centre (on a log scale) of the interval. Also successive estimates of 1.24 (0.91-1.61) and 1.24 (0.91-1.54) have the same RR and lower confidence limit, but different upper confidence limits;
- although there are slight differences in the estimates presented, we both agree that little association is evident in studies AGABI1, AGABI2 and GILLIL;
- we both also agree that there is some evidence of an association in 4 to 6 year olds but not in 7 to 11 year olds in NHANE3 (referred to as Mannino et al., 2001 in Table 6.34). However, we are at a loss to explain where the estimate of 3.20 (1.34-5.68) for 4 to 6 year olds derived from. The data for ever asthma, presented only graphically in the source paper, give a RR of order 2 or 3, but one that is not significant as the lower error bar clearly overlaps 1. It is also noteworthy that the source states that though analysis separating effects of ETS exposure (measured by cotinine) and prenatal maternal smoking was conducted for 7-11 year olds, it "*yielded no significant results (data not shown);"* and
- two of the three studies cited in Table 6.34 as providing significant results for postnatal only exposure were not included in our Table 9.17. The results from the TAYLOR study presented by Neuspiel et al. (1989) were not used by us as they related to "wheezy bronchitis" not asthma. In any case, the data presented in the source paper give RRs of 2.16, 1.46 and 0.80 for postnatal only exposure (depending on when the exposure had occurred) and it is not apparent why Table 6.34 cites a RR of 2.30 (1.26-4.22) which is higher than any of these. The results from the AZIZI study (Azizi et al., 1995), of 1.91 (1.13-3.21) are for "sharing bedroom with smoker," whereas results for paternal smoking only were stated to be not associated with increased risk for respiratory symptoms. We had not included a result for AZIZI in our Table 9.17 as results for *in utero* exposure had not been reported. However, it is true that no mothers reported smoking so that, assuming that the mothers had never smoked, it could have been included, along with other similar studies mentioned in §9.3.6.

Overall, the data presented by the California EPA in Table 6.34, and the conclusions drawn from them, must be regarded as dubious.

The updated report also contains no discussion on how effects of induction and exacerbation might be distinguished. Nor does it make clear that the number of studies which provide data specific to asthma induction is very limited.

9.5.4. Conclusions

The overall data are consistent with some effect of parental smoking on risk of asthma in the child. However, the lack of a significant association with in-life only exposure and with smoking by the father only (and more generally with smoking by other household members except the mother) argues against ETS exposure being responsible. The pattern of results fits in much better with a role of exposure during gestation, though the possibility of some effect of ETS cannot be excluded. The increased risk of asthma seen where the mother smokes postnatally can reasonably be attributed to the fact that many of these mothers would also have smoked in pregnancy. The tendency seen in some analyses for risk to be increased where the father smokes can also reasonably be attributed to the strong correlation between smoking by parents, so that children born to fathers who smoke would be more likely to have mothers who smoked postnatally and in pregnancy. Evidence related to parental ex-smoking is very limited and inconclusive.

Our meta-analyses have deliberately excluded studies of asthmatic children which relate specifically to asthma exacerbation. As such, one cannot make inferences regarding asthma exacerbation from the data presented. However, it should be noted that there are difficulties in interpreting all the evidence presented here strictly in terms of asthma induction, and indeed the number of studies that relate onset of asthma to previous in-life exposure of the child to smoking by parents (or other household members) is very limited, with none of these separating out potential effects of in-life and *in utero* exposure.

Our conclusion that the available evidence does not clearly demonstrate any causal effect of ETS exposure, and suggests strongly that smoking in pregnancy is responsible for most, if not all, of the association seen between asthma and smoking by parents or household members, is not inconsistent with the view expressed by Strachan and Cook (Strachan & Cook, 1998) that ETS is not *"a cause of the underlying asthmatic tendency,"* but conflicts with the conclusion of the California EPA (National Cancer Institute, 1999; California EPA, 2005) that ETS induces asthma. We show that there are considerable weaknesses in the California EPA reports.

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Table C1. Children - Meta-analysis of Exposure during Lifetime, Biochemical/Total (or nearest equivalent), Lifetime Asthma

This analysis is restricted to results for:
1) Lifetime asthma
2) Biochemical, total, household (overall), or parental exposure
3) Exposure during child's lifetime (also including parent ever smoker, but not specific in utero exposure or specific discontinued exposure)
4) Results not by amount of exposure
5) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
6) EXPOS : biochemical, total, household, parent
7) BIOMEA : saliva, blood, urine
8) WHOPAR : any/unspecified parent, mother regardless of father, mother only, father regardless of mother, father only
9) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
10) UNEXSO : not specific parent, neither parent, none in household, none
11) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
12) UNEXHI : not exposed defined as smoked none, or smoked none+low
13) RACE : all in study or nearest available, otherwise by race
14) ONSET : yes, no (prevalence)
15) For overlapping studies: principal rather than subsidiary studies
Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	110
NS	104
Wt	6026.92
Het Chi	293.19
Het df	109
Het P	***
Fixed RR	1.20
RRl	1.17
RRu	1.23
P	+++
Random RR	1.23
RRl	1.17
RRu	1.29
P	+++
Asymm P	(*)

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N	97	7	6	13	19	78	5	13	27	51	14
Het P	***	(*)	N.S.	***	*	***	N.S.	N.S.	(*)	***	***
Fixed RR	1.20	1.18	1.06	1.25	1.27	1.16	1.23	1.24	1.27	1.14	1.23
RRl	1.17	1.03	0.90	1.08	1.21	1.13	1.08	1.14	1.19	1.10	1.17
RRu	1.23	1.36	1.23	1.46	1.33	1.20	1.41	1.35	1.36	1.19	1.29
P	+++	+	N.S.	++	+++	+++	++	+++	+++	+++	+++
Between P	N.S.			**			*				

	Publication year				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	16	18	33	43	110	3	49	15	9	0
Het P	*	N.S.	**	***	***	N.S.	***	***	*	
Fixed RR	1.14	1.22	1.23	1.18	1.20	1.32	1.25	0.96	1.13	

RRl	1.03	1.14	1.17	1.14	1.17	1.03	1.20	0.90	1.05				
RRu	1.27	1.31	1.29	1.22	1.23	1.69	1.29	1.03	1.22				
P	++	+++	+++	+++	+++	+	+++	N.S.	+++				
Between P	N.S.				***								
	Country in Europe						*Country in Asia*			*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	FarEast	Cent/SE	MidlEast	0-9	10-14	15+	unknown
N	12	6	7	9	8	7	7	2	6	23	42	44	1
Het P	**	N.S.	N.S.	**	N.S.	N.S.	(*)	*	N.S.	**	***	***	N.S.
Fixed RR	1.26	1.39	1.10	1.26	1.11	1.31	0.87	1.75	1.31	1.25	1.24	1.11	1.18
RRl	1.21	1.23	0.97	1.11	1.01	1.18	0.81	1.10	1.14	1.17	1.20	1.06	0.62
RRu	1.33	1.57	1.25	1.44	1.23	1.46	0.94	2.79	1.51	1.33	1.29	1.16	2.24
P	+++	+++	N.S.	+++	+	+++	---	+	+++	+++	+++	+++	N.S.
Between P	*						***			***			
	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	24	56	22	3	5	10	72	3	25	22	9	79	64	46
Het P	(*)	***	N.S.	N.S.	(*)	**	***	N.S.	***	N.S.	N.S.	***	***	**
Fixed RR	1.22	1.15	1.29	1.16	1.07	1.03	1.17	1.31	1.27	1.10	1.26	1.21	1.18	1.24
RRl	1.14	1.11	1.23	0.91	0.91	0.95	1.13	1.24	1.20	1.02	1.15	1.17	1.14	1.18
RRu	1.31	1.19	1.35	1.47	1.26	1.11	1.21	1.38	1.35	1.18	1.38	1.24	1.22	1.29
P	+++	+++	+++	N.S.	N.S.	N.S.	+++	+++	+++	+	+++	+++	+++	+++
Between P	**					***				*			(*)	
	Respondent for diagnosis				*Questionnaire for symptoms*			*Analysis type*		*Number of cases (lifetime asthma)*				
	medrec	parent	child	mixed	ISAAC	ATS	other	prevlnce	onset	1-50	51-100	101-200	201+	unknown
N	12	70	15	13	22	12	76	95	15	13	16	27	52	2
Het P	N.S.	***	**	***	***	N.S.	***	***	(*)	(*)	(*)	**	***	N.S.
Fixed RR	1.30	1.17	1.04	1.38	1.03	1.25	1.28	1.17	1.27	1.53	1.41	1.20	1.18	1.38
RRl	1.23	1.13	0.97	1.26	0.99	1.15	1.24	1.14	1.21	1.20	1.22	1.10	1.15	1.01
RRu	1.37	1.21	1.12	1.50	1.08	1.37	1.32	1.21	1.33	1.95	1.62	1.30	1.22	1.88
P	+++	+++	N.S.	+++	N.S.	+++	+++	+++	+++	+++	+++	+++	+++	+
Between P	***				***			**		*				
	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	49	61	28	82	16	94	22	88	30	80	38	72	19	91
Het P	***	***	**	***	**	***	*	***	***	***	*	***	N.S.	***
Fixed RR	1.23	1.18	1.18	1.20	1.25	1.19	1.17	1.20	1.22	1.19	1.23	1.18	1.25	1.19
RRl	1.18	1.14	1.12	1.17	1.16	1.16	1.10	1.17	1.15	1.16	1.18	1.15	1.17	1.16
RRu	1.28	1.22	1.25	1.24	1.34	1.22	1.24	1.24	1.29	1.23	1.29	1.22	1.34	1.22
P	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.		N.S.	

Table C1. Continued

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	14	96	18	92	15	95	36	74	5	105	18	92
Het P	(*)	***	***	***	***	***	***	***	(*)	***	*	***
Fixed RR	1.32	1.18	1.37	1.18	1.40	1.18	1.21	1.19	1.03	1.20	1.23	1.19
RRl	1.23	1.15	1.27	1.15	1.29	1.15	1.15	1.16	0.88	1.17	1.16	1.16
RRu	1.42	1.21	1.48	1.21	1.53	1.21	1.28	1.23	1.19	1.23	1.31	1.22
P	+++	+++	+++	+++	+++	+++	+++	+++	N.S.	+++	+++	+++
Between P	**		***		***		N.S.		*		N.S.	

	Exposed group : Source/who is smoker						*Exposed group : when exposed*				
	Biochem	TotETS	AnyHh	AnyPar	Mother	Father	lif/ev	age<7y	current	unspec	other
N	2	5	47	21	32	3	25	8	33	39	5
Het P	N.S.	(*)	***	N.S.	**	N.S.	*	***	***	***	(*)
Fixed RR	1.36	1.18	1.09	1.21	1.31	1.19	1.24	1.23	1.28	1.10	1.27
RRl	0.97	1.04	1.05	1.12	1.26	0.93	1.19	1.12	1.21	1.05	1.06
RRu	1.91	1.35	1.14	1.31	1.36	1.54	1.30	1.35	1.35	1.14	1.52
P	(+)	+	+++	+++	+++	N.S.	+++	+++	+++	+++	++
Between P	***						***				

	Unexposed group : who is smoker			*Unexposed group : time*				*Number of adjustment variables*					
	NoHhMem	NoParent	NotSpPar	non	never	non+othr	NA	0	1	2	3-5	6-9	10+
N	54	23	33	95	13	0	2	53	14	6	14	18	5
Het P	***	N.S.	**	***	N.S.		N.S.	***	*	***	***	N.S.	N.S.
Fixed RR	1.10	1.21	1.31	1.16	1.30		1.36	1.16	1.19	1.38	1.14	1.32	1.15
RRl	1.06	1.12	1.26	1.13	1.23		0.97	1.12	1.08	1.27	1.05	1.22	0.98
RRu	1.14	1.30	1.36	1.20	1.36		1.91	1.20	1.32	1.49	1.24	1.42	1.34
P	+++	+++	+++	+++	+++		(+)	+++	+++	+++	++	+++	(+)
Between P	***			***				***					

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	32	78	25	85	7	103	52	58	41	35	14	20
Het P	**	***	*	***	**	***	***	***	***	***	N.S.	***
Fixed RR	1.25	1.18	1.15	1.21	1.19	1.20	1.27	1.16	1.26	1.08	1.10	1.26
RRl	1.19	1.14	1.08	1.17	1.05	1.17	1.22	1.12	1.21	1.03	0.99	1.21
RRu	1.32	1.21	1.22	1.24	1.34	1.23	1.33	1.19	1.32	1.13	1.22	1.32
P	+++	+++	+++	+++	++	+++	+++	+++	+++	++	(+)	+++
Between P	*		N.S.		N.S.		***		***			

Table C3. Children - Meta-analysis of Exposure during Lifetime, Biochemical/Total (or nearest equivalent), Current Asthma

This analysis is restricted to results for:
1) Current asthma
2) Biochemical, total, household (overall), or parental exposure
3) Exposure during child's lifetime (also including parent ever smoker, but not specific in utero exposure or specific discontinued exposure)
4) Results not by amount of exposure
5) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
6) EXPOS : biochemical, total, household, parent
7) BIOMEA : saliva, blood, urine
8) WHOPAR : any/unspecified parent, mother regardless of father, mother only, father regardless of mother, father only
9) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
10) UNEXSO : not specific parent, neither parent, none in household, none
11) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
12) UNEXHI : not exposed defined as smoked none, or smoked none+low
13) RACE : all in study or nearest available, otherwise by race
14) For overlapping studies: principal rather than subsidiary studies, and for prospective studies, most recent follow-up

Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	87
NS	85
Wt	7866.91
Het Chi	294.93
Het df	86
Het P	***
Fixed RR	1.17
RRl	1.15
RRu	1.20
P	+++
Random RR	1.20
RRl	1.13
RRu	1.27
P	+++
Asymm P	N.S.

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N	83	2	2	24	9	54	0	5	17	55	10
Het P	***	***	N.S.	N.S.	(*)	***		N.S.	***	***	N.S.
Fixed RR	1.17	0.94	0.64	1.32	1.04	1.17		0.96	1.24	1.16	1.49
RRl	1.15	0.58	0.32	1.23	0.93	1.14		0.81	1.15	1.14	1.29
RRu	1.20	1.52	1.27	1.43	1.17	1.19		1.13	1.33	1.19	1.73
P	+++	N.S.	N.S.	+++	N.S.	+++		N.S.	+++	+++	+++
Between P	N.S.			***			***				

Table C3. Continued

	Publication year				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	3	16	34	34	15	3	40	23	2	4
Het P	(*)	**	***	***	***	N.S.	***	***	*	N.S.
Fixed RR	0.77	1.26	1.11	1.31	1.38	1.46	1.16	1.11	1.18	1.77
RRl	0.48	1.15	1.08	1.26	1.31	1.13	1.10	1.08	0.73	1.27
RRu	1.24	1.38	1.14	1.36	1.45	1.90	1.23	1.14	1.89	2.47
P	N.S.	+++	+++	+++	+++	++	+++	+++	N.S.	+++
Between P	***				***					

	Country in Europe						*Country in Asia*			*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	FarEast	Cent/SE	MidlEast	0-9	10-14	15+	unknown
N	5	3	9	12	7	4	14	5	4	21	32	33	1
Het P	N.S.	N.S.	N.S.	**	*	*	***	N.S.	N.S.	*	***	***	N.S.
Fixed RR	1.16	1.21	1.20	1.23	1.04	1.03	1.09	1.56	1.16	1.30	1.28	1.10	1.96
RRl	0.90	1.08	1.08	1.10	0.93	0.81	1.06	1.33	0.94	1.19	1.23	1.07	1.10
RRu	1.49	1.37	1.33	1.38	1.18	1.30	1.13	1.82	1.44	1.41	1.33	1.14	3.48
P	N.S.	++	+++	+++	N.S.	N.S.	+++	+++	N.S.	+++	+++	+++	+
Between P	N.S.						***			***			

	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	8	57	21	1	0	14	56	0	17	11	15	61	32	55
Het P	**	***	N.S.	N.S.		***	***		**	**	***	***	**	***
Fixed RR	1.21	1.17	1.24	3.33		1.35	1.13		1.12	1.08	1.16	1.22	1.19	1.17
RRl	1.08	1.14	1.12	0.78		1.28	1.10		1.02	0.99	1.13	1.17	1.09	1.15
RRu	1.36	1.20	1.38	14.23		1.41	1.16		1.22	1.19	1.19	1.27	1.30	1.20
P	+++	+++	+++	N.S.		+++	+++		+	(+)	+++	+++	+++	+++
Between P	N.S.					***				*			N.S.	

	Respondent for diagnosis				*Questionnaire for symptoms*			*Number of cases (current asthma)*				
	medrec	parent	child	mixed	ISAAC	ATS	other	1-50	51-100	101-200	201+	unknown
N	17	45	19	6	23	9	55	16	17	20	31	3
Het P	N.S.	***	***	**	***	*	***	N.S.	**	**	***	N.S.
Fixed RR	1.33	1.20	1.16	1.00	1.17	1.06	1.19	1.31	1.03	1.06	1.19	1.40
RRl	1.16	1.15	1.13	0.83	1.15	0.94	1.13	1.06	0.90	0.99	1.16	1.03
RRu	1.52	1.25	1.19	1.22	1.20	1.19	1.26	1.62	1.18	1.15	1.21	1.90
P	+++	+++	+++	N.S.	+++	N.S.	+++	+	N.S.	N.S.	+++	+
Between P	(*)				N.S.			*				

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	58	29	49	38	13	74	33	54	33	54	31	56	15	72
Het P	***	***	***	***	***	***	***	***	***	***	***	***	*	***
Fixed RR	1.17	1.24	1.13	1.36	1.38	1.12	1.12	1.34	1.17	1.21	1.33	1.12	1.12	1.18
RRl	1.14	1.13	1.10	1.30	1.31	1.10	1.09	1.28	1.14	1.14	1.28	1.09	1.02	1.15
RRu	1.20	1.36	1.15	1.43	1.45	1.15	1.15	1.39	1.20	1.27	1.39	1.15	1.22	1.21
P	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+	+++
Between P	N.S.		***		***		***		N.S.		***		N.S.	

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	25	62	22	65	20	67	21	66	9	78	21	66
Het P	***	***	***	***	***	***	***	***	(*)	***	**	***
Fixed RR	1.17	1.19	1.17	1.17	1.22	1.17	1.46	1.12	1.11	1.18	1.22	1.17
RRl	1.14	1.14	1.10	1.15	1.15	1.14	1.38	1.10	1.02	1.15	1.14	1.14
RRu	1.20	1.24	1.25	1.20	1.30	1.20	1.54	1.15	1.21	1.21	1.30	1.20
P	+++	+++	+++	+++	+++	+++	+++	+++	+	+++	+++	+++
Between P	N.S.		N.S.		N.S.		***		N.S.		N.S.	

	Exposed group : Source/who is smoker						*Exposed group : when exposed*				
	Biochem	TotETS	AnyHh	AnyPar	Mother	Father	lif/ev	age<7y	current	unspec	other
N	2	3	43	19	18	2	11	9	26	38	3
Het P	N.S.	***	***	N.S.	***	N.S.	*	(*)	***	***	N.S.
Fixed RR	1.34	1.45	1.12	1.24	1.20	1.01	1.06	1.33	1.16	1.18	1.41
RRl	0.83	1.37	1.09	1.14	1.11	0.69	0.95	1.16	1.10	1.15	1.03
RRu	2.16	1.54	1.15	1.35	1.30	1.48	1.17	1.53	1.22	1.21	1.93
P	N.S.	+++	+++	+++	+++	N.S.	N.S.	+++	+++	+++	+
Between P	***						(*)				

	Unexposed group : who is smoker			*Unexposed group : time*				*Number of adjustment variables*					
	NoHhMem	NoParent	NotSpPar	non	never	non+othr	NA	0	1	2	3-5	6-9	10+
N	50	19	18	78	6	1	2	33	3	6	12	22	11
Het P	***	N.S.	**	***	**	N.S.	N.S.	**	N.S.	**	**	***	*
Fixed RR	1.17	1.24	1.19	1.18	1.10	2.36	1.34	1.17	1.08	1.16	1.25	1.17	1.17
RRl	1.14	1.14	1.10	1.15	1.00	0.91	0.83	1.09	0.81	1.06	1.09	1.14	1.08
RRu	1.19	1.35	1.29	1.20	1.21	6.11	2.16	1.26	1.44	1.26	1.43	1.20	1.27
P	+++	+++	+++	+++	+	(+)	N.S.	+++	N.S.	+++	++	+++	+++
Between P	N.S.			N.S.				N.S.					

Table C3. Continued

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	45	42	36	51	13	74	46	41	39	17	9	22
Het P	***	***	***	***	N.S.	***	***	***	***	*	(*)	***
Fixed RR	1.18	1.14	1.12	1.35	1.26	1.17	1.18	1.17	1.13	1.17	1.08	1.36
RRl	1.15	1.07	1.09	1.29	1.17	1.14	1.15	1.10	1.10	1.07	0.91	1.29
RRu	1.20	1.23	1.15	1.41	1.36	1.19	1.20	1.23	1.16	1.28	1.27	1.42
P	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	N.S.	+++
Between P	N.S.		***		(*)		N.S.		***			

Table C5. Children - Meta-analysis of Parental Exposure during Lifetime, Any Parent (or Mother, or Father, if Any not available), Lifetime Asthma

This analysis is restricted to results for:
1) Lifetime asthma
2) Parental exposure
3) Exposure during child's lifetime (also including parent ever smoker, but not specific in utero exposure or specific discontinued exposure)
4) Results not by amount of exposure
5) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
6) WHOPAR : any/unspecified parent, mother regardless of father, mother only, father regardless of mother, father only
7) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
8) UNEXSO : not specific parent, neither parent, none in household
9) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
10) UNEXHI : not exposed defined as smoked none, or smoked none+low
11) RACE : all in study or nearest available, otherwise by race
12) ONSET : yes, no (prevalence)
13) For overlapping studies: principal rather than subsidiary studies

Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	72
NS	68
Wt	3673.07
Het Chi	109.15
Het df	71
Het P	**
Fixed RR	1.27
RRl	1.23
RRu	1.32
P	+++
Random RR	1.27
RRl	1.21
RRu	1.33
P	+++
Asymm P	N.S.

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N	63	5	4	9	15	48	5	10	21	26	10
Het P	***	N.S.	N.S.	*	N.S.	*	N.S.	(*)	(*)	(*)	*
Fixed RR	1.28	1.34	1.18	1.26	1.28	1.27	1.23	1.23	1.32	1.27	1.28
RRl	1.23	1.09	0.93	1.06	1.22	1.22	1.08	1.12	1.22	1.19	1.21
RRu	1.32	1.64	1.50	1.50	1.34	1.33	1.41	1.34	1.42	1.36	1.35
P	+++	++	N.S.	++	+++	+++	++	+++	+++	+++	+++
Between P	N.S.			N.S.			N.S.				

Table C5. Continued

	Publication year				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	14	15	20	23	22	2	31	12	5	0
Het P	**	N.S.	N.S.	*	N.S.	N.S.	***	N.S.	*	
Fixed RR	1.18	1.26	1.32	1.28	1.33	1.27	1.28	1.23	1.18	
RRl	1.07	1.16	1.23	1.23	1.23	0.98	1.23	1.10	1.06	
RRu	1.31	1.36	1.42	1.34	1.44	1.63	1.33	1.37	1.32	
P	++	+++	+++	+++	+++	(+)	+++	+++	++	
Between P	N.S.				N.S.					

	Country in Europe						*Country in Asia*			*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	FarEast	Cent/SE	MidlEast	0-9	10-14	15+	unknown
N	11	2	3	8	5	2	5	1	6	16	27	28	1
Het P	**	N.S.	*	(*)	N.S.	N.S.	N.S.	N.S.	N.S.	*	**	N.S.	N.S.
Fixed RR	1.28	1.47	1.12	1.31	1.15	1.21	1.07	0.79	1.36	1.30	1.26	1.29	1.24
RRl	1.22	1.26	0.94	1.15	0.94	0.99	0.89	0.42	1.18	1.20	1.21	1.21	0.72
RRu	1.35	1.72	1.34	1.49	1.41	1.47	1.29	1.47	1.57	1.41	1.32	1.37	2.14
P	+++	+++	N.S.	+++	N.S.	(+)	N.S.	N.S.	+++	+++	+++	+++	N.S.
Between P	N.S.						*			N.S.			

	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	19	31	17	2	3	6	46	3	17	16	8	48	38	34
Het P	*	*	N.S.	N.S.	N.S.	(*)	**	N.S.	N.S.	N.S.	N.S.	**	*	*
Fixed RR	1.23	1.28	1.32	1.15	1.13	1.02	1.28	1.31	1.28	1.18	1.32	1.28	1.29	1.25
RRl	1.14	1.21	1.25	0.88	0.96	0.89	1.22	1.24	1.18	1.05	1.19	1.23	1.24	1.19
RRu	1.32	1.35	1.39	1.49	1.33	1.17	1.35	1.38	1.39	1.32	1.46	1.33	1.35	1.32
P	+++	+++	+++	N.S.	N.S.	N.S.	+++	+++	+++	++	+++	+++	+++	+++
Between P	N.S.					*				N.S.			N.S.	

	Respondent for diagnosis				*Questionnaire for symptoms*			*Analysis type*		*Number of cases (lifetime asthma)*				
	medrec	parent	child	mixed	ISAAC	ATS	other	prevlnce	onset	1-50	51-100	101-200	201+	unknown
N	11	44	10	7	13	10	49	60	12	7	12	17	34	2
Het P	N.S.	(*)	(*)	N.S.	N.S.	N.S.	***	**	(*)	N.S.	N.S.	*	*	N.S.
Fixed RR	1.30	1.31	1.05	1.24	1.17	1.29	1.30	1.28	1.27	1.44	1.55	1.20	1.27	1.38
RRl	1.23	1.25	0.94	1.12	1.09	1.17	1.25	1.23	1.20	1.04	1.33	1.08	1.22	1.01
RRu	1.37	1.37	1.17	1.38	1.26	1.41	1.36	1.33	1.33	2.01	1.82	1.34	1.31	1.88
P	+++	+++	N.S.	+++	+++	+++	+++	+++	+++	+	+++	+++	+++	+
Between P	**				*			N.S.		(*)				

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	33	39	17	55	9	63	14	58	21	51	23	49	11	61
Het P	(*)	**	N.S.	**	N.S.	**	N.S.	**	**	*	N.S.	**	N.S.	**
Fixed RR	1.30	1.26	1.25	1.28	1.35	1.27	1.22	1.29	1.26	1.28	1.26	1.28	1.28	1.27
RRl	1.23	1.21	1.16	1.23	1.22	1.22	1.13	1.24	1.18	1.23	1.19	1.23	1.18	1.23
RRu	1.38	1.31	1.36	1.32	1.49	1.31	1.32	1.33	1.35	1.33	1.34	1.33	1.38	1.32
P	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.		N.S.	

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	7	65	11	61	10	62	24	48	2	70	15	57
Het P	(*)	**	N.S.	**	N.S.	**	(*)	**	**	**	N.S.	**
Fixed RR	1.28	1.27	1.23	1.28	1.27	1.28	1.28	1.27	1.22	1.28	1.33	1.26
RRl	1.18	1.23	1.11	1.24	1.13	1.23	1.20	1.23	0.78	1.23	1.24	1.22
RRu	1.40	1.32	1.36	1.32	1.43	1.32	1.37	1.32	1.91	1.32	1.42	1.31
P	+++	+++	+++	+++	+++	+++	+++	+++	N.S.	+++	+++	+++
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.	

	Exposed group : who is smoker			*Exposed group : when exposed*				
	AnyPar	Mother	Father	lif/ev	age<7y	current	unspec	other
N	23	44	5	23	7	18	22	2
Het P	N.S.	**	N.S.	(*)	***	(*)	N.S.	(*)
Fixed RR	1.21	1.30	1.02	1.27	1.27	1.25	1.30	1.27
RRl	1.12	1.26	0.85	1.21	1.15	1.16	1.22	0.98
RRu	1.31	1.35	1.23	1.34	1.40	1.34	1.39	1.65
P	+++	+++	N.S.	+++	+++	+++	+++	(+)
Between P	*			N.S.				

Table C5. Continued

	Unexposed group : who is smoker			*Unexposed group : time*				*Number of adjustment variables*					
	NoHhMem	NoParent	NotSpPar	non	never	non+othr	NA	0	1	2	3-5	6-9	10+
N	3	24	45	58	14	0	0	34	11	3	10	12	2
Het P	N.S.	N.S.	***	**	N.S.			(*)	*	N.S.	*	N.S.	N.S.
Fixed RR	0.97	1.21	1.30	1.26	1.31			1.26	1.32	1.37	1.27	1.30	1.28
RRl	0.76	1.12	1.25	1.20	1.24			1.21	1.14	1.21	1.14	1.19	1.00
RRu	1.24	1.30	1.35	1.31	1.37			1.31	1.52	1.56	1.43	1.41	1.63
P	N.S.	+++	+++	+++	+++			+++	+++	+++	+++	+++	(+)
Between P	*			N.S.				N.S.					

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	23	49	15	57	5	67	34	38	30	17	13	12
Het P	*	*	N.S.	**	N.S.	**	**	N.S.	*	N.S.	N.S.	*
Fixed RR	1.32	1.26	1.24	1.28	1.46	1.27	1.32	1.25	1.25	1.34	1.17	1.30
RRl	1.23	1.22	1.12	1.24	1.23	1.23	1.25	1.21	1.18	1.23	1.05	1.23
RRu	1.41	1.31	1.37	1.32	1.75	1.31	1.39	1.30	1.32	1.45	1.31	1.36
P	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	++	+++
Between P	N.S.		N.S.		N.S.		N.S.		N.S.			

Table C7. Children - Meta-analysis of Parental Exposure during Lifetime, Any Parent (or Mother, or Father, if Any not available), Current Asthma

This analysis is restricted to results for:
1) Current asthma
2) Parental exposure
3) Exposure during child's lifetime (also including parent ever smoker, but not specific in utero exposure or specific discontinued exposure)
4) Results not by amount of exposure
5) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
6) WHOPAR : any/unspecified parent, mother regardless of father, mother only, father regardless of mother, father only
7) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
8) UNEXSO : not specific parent, neither parent, none in household
9) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
10) UNEXHI : not exposed defined as smoked none, or smoked none+low
11) RACE : all in study or nearest available, otherwise by race
12) For overlapping studies: principal rather than subsidiary studies, and for prospective studies, most recent follow-up

Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	45
NS	45
Wt	1190.84
Het Chi	80.44
Het df	44
Het P	***
Fixed RR	1.21
RRl	1.14
RRu	1.28
P	+++
Random RR	1.21
RRl	1.11
RRu	1.33
P	+++
Asymm P	N.S.

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N	45	0	0	15	4	26	0	3	11	27	4
Het P	***			(*)	N.S.	**		(*)	N.S.	*	N.S.
Fixed RR	1.21			1.29	1.04	1.20		0.95	1.40	1.18	1.26
RRl	1.14			1.17	0.90	1.11		0.80	1.24	1.09	1.02
RRu	1.28			1.41	1.22	1.30		1.13	1.57	1.27	1.56
P	+++			+++	N.S.	+++		N.S.	+++	+++	+
Between P	N.S.			(*)			**				

Table C7. Continued

	Publication year				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	3	12	15	15	9	2	19	11	2	2
Het P	(*)	**	N.S.	*	N.S.	N.S.	**	*	*	N.S.
Fixed RR	0.77	1.18	1.28	1.13	1.19	1.47	1.19	1.16	1.18	1.68
RRl	0.48	1.06	1.18	1.01	1.08	1.13	1.09	1.00	0.73	1.13
RRu	1.24	1.33	1.39	1.26	1.32	1.92	1.29	1.36	1.89	2.51
P	N.S.	++	+++	+	+++	++	+++	(+)	N.S.	+
Between P	(*)				N.S.					

	Country in Europe						*Country in Asia*			*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	FarEast	Cent/SE	MidlEast	0-9	10-14	15+	unknown
N	4	3	0	7	4	1	7	0	4	12	13	19	1
Het P	N.S.	N.S.		**	*	N.S.	*		N.S.	(*)	N.S.	**	N.S.
Fixed RR	1.13	1.21		1.14	1.25	1.22	1.14		1.20	1.36	1.10	1.23	1.96
RRl	0.88	1.08		0.98	0.96	0.74	0.92		0.95	1.20	1.01	1.12	1.10
RRu	1.46	1.37		1.33	1.63	2.01	1.40		1.52	1.53	1.20	1.36	3.48
P	N.S.	++		(+)	(+)	N.S.	N.S.		N.S.	+++	+	+++	+
Between P	N.S.						N.S.			*			

	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	6	26	12	1	0	6	27	0	12	7	8	30	18	27
Het P	*	*	*	N.S.		**	*		(*)	**	N.S.	*	**	*
Fixed RR	1.15	1.20	1.32	3.33		1.22	1.21		1.19	1.15	1.13	1.26	1.22	1.20
RRl	1.01	1.11	1.14	0.78		1.02	1.12		1.07	1.00	1.01	1.17	1.08	1.13
RRu	1.31	1.28	1.52	14.23		1.47	1.30		1.33	1.34	1.25	1.36	1.39	1.28
P	+	+++	+++	N.S.		+	+++		+++	(+)	+	+++	++	+++
Between P	N.S.					N.S.				N.S.			N.S.	

	Respondent for diagnosis				*Questionnaire for symptoms*			*Number of cases (current asthma)*				
	medrec	parent	child	mixed	ISAAC	ATS	other	1-50	51-100	101-200	201+	unknown
N	12	23	10	0	9	2	34	8	10	11	15	1
Het P	*	N.S.	**		N.S.	N.S.	***	N.S.	(*)	**	(*)	N.S.
Fixed RR	1.41	1.20	1.10		1.29	1.00	1.20	1.17	1.17	1.17	1.22	3.27
RRl	1.19	1.12	0.96		1.17	0.85	1.11	0.89	0.98	1.03	1.14	1.13
RRu	1.66	1.29	1.26		1.42	1.18	1.30	1.55	1.41	1.32	1.31	9.48
P	+++	+++	N.S.		+++	N.S.	+++	N.S.	(+)	+	+++	+
Between P	(*)				*			N.S.				

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	31	14	26	19	7	38	16	29	17	28	15	30	8	37
Het P	**	(*)	***	N.S.	N.S.	***	**	*	*	**	(*)	**	*	*
Fixed RR	1.18	1.32	1.18	1.26	1.18	1.22	1.18	1.25	1.18	1.26	1.19	1.23	1.10	1.27
RRl	1.11	1.16	1.10	1.14	1.07	1.14	1.10	1.14	1.10	1.14	1.10	1.13	1.00	1.18
RRu	1.26	1.50	1.26	1.40	1.31	1.30	1.27	1.37	1.26	1.38	1.28	1.33	1.21	1.36
P	+++	+++	+++	+++	++	+++	+++	+++	+++	+++	+++	+++	+	+++
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.		*	

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	7	38	8	37	6	39	10	35	6	39	14	31
Het P	*	**	N.S.	***	N.S.	***	N.S.	***	N.S.	***	N.S.	**
Fixed RR	1.21	1.21	1.24	1.18	1.33	1.19	1.22	1.20	1.20	1.21	1.29	1.14
RRl	1.10	1.12	1.13	1.10	1.13	1.12	1.04	1.13	1.08	1.13	1.19	1.05
RRu	1.32	1.30	1.37	1.27	1.55	1.26	1.44	1.28	1.35	1.29	1.41	1.23
P	+++	+++	+++	+++	+++	+++	+	+++	++	+++	+++	++
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		*	

	Exposed group : who is smoker			*Exposed group : when exposed*				
	AnyPar	Mother	Father	lif/ev	age<7y	current	unspec	other
N	19	23	3	11	2	14	17	1
Het P	N.S.	***	N.S.	*	N.S.	(*)	*	N.S.
Fixed RR	1.24	1.20	0.90	1.04	1.64	1.22	1.27	1.47
RRl	1.14	1.11	0.65	0.92	1.22	1.13	1.13	0.97
RRu	1.35	1.30	1.24	1.17	2.21	1.33	1.42	2.23
P	+++	+++	N.S.	N.S.	++	+++	+++	(+)
Between P	N.S.			*				

Table C7. Continued

	Unexposed group : who is smoker			*Unexposed group : time*				*Number of adjustment variables*					
	NoHhMem	NoParent	NotSpPar	non	never	non+othr	NA	0	1	2	3-5	6-9	10+
N	5	19	21	38	7	0	0	21	3	0	9	7	5
Het P	N.S.	N.S.	***	*	**			*	N.S.		*	**	N.S.
Fixed RR	0.90	1.24	1.20	1.27	1.10			1.24	1.09		1.28	1.20	1.17
RRl	0.64	1.14	1.10	1.18	1.01			1.11	0.83		1.10	1.05	1.07
RRu	1.26	1.35	1.29	1.36	1.21			1.39	1.45		1.50	1.37	1.28
P	N.S.	+++	+++	+++	+			+++	N.S.		++	++	+++
Between P	N.S.			*				N.S.					

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	21	24	16	29	8	37	22	23	15	10	7	13
Het P	**	*	**	*	N.S.	***	**	*	N.S.	N.S.	*	**
Fixed RR	1.20	1.22	1.17	1.26	1.28	1.16	1.20	1.23	1.28	1.30	1.16	1.08
RRl	1.12	1.10	1.08	1.16	1.17	1.08	1.12	1.10	1.18	1.12	0.96	0.98
RRu	1.28	1.35	1.26	1.38	1.39	1.25	1.28	1.37	1.39	1.51	1.40	1.20
P	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	N.S.	N.S.
Between P	N.S.		N.S.		(*)		N.S.		(*)			

Table C25. Children - Meta-analysis of Exposure during Lifetime, Biochemical/Total (or nearest equivalent), Lifetime Asthma (or Current if Lifetime not available)

This analysis is restricted to results for:
1) Biochemical, total, household (overall), or parental exposure
2) Exposure during child's lifetime (also including parent ever smoker, but not specific in utero exposure or specific discontinued exposure)
3) Results not by amount of exposure
4) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
5) ASTHMA : lifetime, current
6) EXPOS : biochemical, total, household, parent
7) BIOMEA : saliva, blood, urine
8) WHOPAR : any/unspecified parent, mother regardless of father, mother only, father regardless of mother, father only
9) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
10) UNEXSO : not specific parent, neither parent, none in household, none
11) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
12) UNEXHI : not exposed defined as smoked none, or smoked none+low
13) RACE : all in study or nearest available, otherwise by race
14) ONSET : yes, no (prevalence)
15) For overlapping studies: principal rather than subsidiary studies, and for prospective studies, most recent follow-up

Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	179
NS	171
Wt	13259.60
Het Chi	553.37
Het df	178
Het P	***
Fixed RR	1.19
RRl	1.17
RRu	1.21
P	+++
Random RR	1.23
RRl	1.18
RRu	1.28
P	+++
Asymm P	*

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N	162	9	8	37	25	117	5	14	41	95	24
Het P	***	**	N.S.	**	**	***	N.S.	(*)	***	***	***
Fixed RR	1.19	1.16	1.03	1.31	1.25	1.17	1.23	1.23	1.25	1.16	1.25
RRl	1.17	1.01	0.89	1.22	1.20	1.15	1.08	1.13	1.19	1.14	1.20
RRu	1.21	1.33	1.20	1.40	1.31	1.19	1.41	1.34	1.32	1.19	1.31
P	+++	+	N.S.	+++	+++	+++	++	+++	+++	+++	+++
Between P	N.S.			***			**				

Table C25. Continued

	Publication year				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	18	33	58	70	43	6	80	36	10	4
Het P	*	(*)	***	***	***	N.S.	***	***	*	N.S.
Fixed RR	1.14	1.27	1.14	1.25	1.39	1.38	1.23	1.08	1.14	1.77
RRl	1.03	1.20	1.11	1.21	1.33	1.16	1.20	1.06	1.06	1.27
RRu	1.26	1.35	1.16	1.28	1.44	1.66	1.27	1.11	1.23	2.47
P	+	+++	+++	+++	+++	+++	+++	+++	+++	+++
Between P	***				***					

	Country in Europe						*Country in Asia*			*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	FarEast	Cent/SE	MidlEast	0-9	10-14	15+	unknown
N	17	9	12	20	12	10	19	7	10	41	67	69	2
Het P	**	N.S.	N.S.	***	(*)	**	***	*	N.S.	***	***	***	N.S.
Fixed RR	1.26	1.30	1.15	1.23	1.13	1.26	1.06	1.57	1.26	1.27	1.28	1.11	1.56
RRl	1.20	1.19	1.06	1.12	1.03	1.14	1.03	1.36	1.12	1.21	1.25	1.08	1.02
RRu	1.32	1.41	1.25	1.34	1.24	1.39	1.09	1.82	1.42	1.34	1.32	1.13	2.40
P	+++	+++	+++	+++	+	+++	+++	+++	+++	+++	+++	+++	+
Between P	N.S.						***			***			

	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	30	98	42	4	5	19	121	3	36	25	20	134	94	85
Het P	**	***	N.S.	N.S.	(*)	***	***	N.S.	***	(*)	***	***	***	***
Fixed RR	1.22	1.17	1.29	1.19	1.07	1.29	1.14	1.31	1.25	1.12	1.17	1.21	1.18	1.20
RRl	1.15	1.15	1.23	0.94	0.91	1.23	1.12	1.24	1.18	1.05	1.14	1.18	1.15	1.17
RRu	1.30	1.19	1.34	1.51	1.26	1.35	1.17	1.38	1.32	1.20	1.21	1.24	1.21	1.22
P	+++	+++	+++	N.S.	N.S.	+++	+++	+++	+++	+++	+++	+++	+++	+++
Between P	***					***				*			N.S.	

	Respondent for diagnosis				*Questionnaire for symptoms*			*Analysis type*		*Number of cases (lifetime/current asthma)*				
	medrec	parent	child	mixed	ISAAC	ATS	other	prevlnce	onset	1-50	51-100	101-200	201+	unknown
N	29	105	27	18	39	20	120	164	15	26	28	44	78	3
Het P	N.S.	***	***	***	***	N.S.	***	***	(*)	N.S.	***	***	***	N.S.
Fixed RR	1.30	1.19	1.15	1.30	1.14	1.22	1.26	1.18	1.27	1.49	1.24	1.13	1.19	1.36
RRl	1.24	1.16	1.12	1.20	1.12	1.13	1.23	1.16	1.21	1.25	1.11	1.06	1.17	1.06
RRu	1.37	1.22	1.18	1.40	1.17	1.32	1.30	1.20	1.33	1.76	1.38	1.19	1.21	1.73
P	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+
Between P	***				***			**		*				

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	91	88	65	114	24	155	49	130	54	125	59	120	27	152
Het P	***	***	***	***	***	***	***	***	***	***	***	***	*	***
Fixed RR	1.19	1.19	1.14	1.24	1.38	1.16	1.13	1.25	1.18	1.20	1.31	1.15	1.23	1.19
RRl	1.17	1.15	1.12	1.21	1.32	1.14	1.10	1.22	1.15	1.17	1.26	1.13	1.16	1.17
RRu	1.22	1.22	1.17	1.27	1.44	1.18	1.16	1.28	1.21	1.24	1.35	1.17	1.30	1.21
P	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Between P	N.S.		***		***		***		N.S.		***		N.S.	

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*		*Asthma definition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	lifetime	current
N	35	144	36	143	32	147	51	128	11	168	35	144	109	70
Het P	***	***	***	***	***	***	***	***	*	***	***	***	***	***
Fixed RR	1.19	1.19	1.24	1.18	1.28	1.18	1.34	1.16	1.10	1.19	1.23	1.18	1.19	1.19
RRl	1.16	1.17	1.18	1.16	1.22	1.16	1.29	1.13	1.02	1.17	1.18	1.16	1.16	1.16
RRu	1.22	1.22	1.31	1.20	1.35	1.20	1.40	1.18	1.19	1.22	1.29	1.21	1.23	1.21
P	+++	+++	+++	+++	+++	+++	+++	+++	+	+++	+++	+++	+++	+++
Between P	N.S.		(*)		**		***		*		N.S.		N.S.	

	Exposed group : Source/who is smoker						*Exposed group : when exposed*				
	Biochem	TotETS	AnyHh	AnyPar	Mother	Father	lif/ev	age<7y	current	unspec	other
N	3	7	80	39	45	5	33	16	51	73	6
Het P	N.S.	***	***	N.S.	***	N.S.	**	***	***	***	(*)
Fixed RR	1.40	1.48	1.11	1.22	1.30	1.14	1.23	1.29	1.23	1.16	1.28
RRl	1.01	1.40	1.09	1.15	1.26	0.92	1.18	1.19	1.19	1.13	1.08
RRu	1.93	1.57	1.14	1.30	1.35	1.40	1.29	1.39	1.28	1.18	1.53
P	+	+++	+++	+++	+++	N.S.	+++	+++	+++	+++	++
Between P	***						**				

Table C25. Continued

	Unexposed group : who is smoker			*Unexposed group : time*				*Number of adjustment variables*					
	NoHhMem	NoParent	NotSpPar	non	never	non+othr	NA	0	1	2	3-5	6-9	10+
N	92	41	46	158	17	1	3	83	16	11	22	34	13
Het P	***	N.S.	***	***	(*)	N.S.	N.S.	***	*	***	***	***	N.S.
Fixed RR	1.15	1.22	1.30	1.18	1.27	2.36	1.40	1.16	1.19	1.33	1.17	1.19	1.21
RRl	1.13	1.15	1.26	1.15	1.21	0.91	1.01	1.13	1.07	1.25	1.09	1.16	1.12
RRu	1.18	1.29	1.35	1.20	1.33	6.11	1.93	1.20	1.31	1.42	1.26	1.22	1.31
P	+++	+++	+++	+++	+++	(+)	+	+++	+++	+++	+++	+++	+++
Between P	***			**				*					

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	63	116	50	129	18	161	85	94	71	50	21	37
Het P	***	***	***	***	*	***	***	***	***	***	N.S.	***
Fixed RR	1.20	1.18	1.13	1.25	1.25	1.19	1.20	1.17	1.16	1.10	1.10	1.32
RRl	1.17	1.14	1.11	1.22	1.17	1.17	1.18	1.13	1.14	1.05	1.01	1.28
RRu	1.23	1.21	1.16	1.28	1.34	1.21	1.23	1.20	1.19	1.15	1.21	1.37
P	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+	+++
Between P	N.S.		***		N.S.		(*)		***			

Table C26. Children - Meta-analysis of Parental Exposure during Lifetime, Any Parent (or Mother, or Father, if Any not available), Lifetime Asthma (or Current if Lifetime not available)

This analysis is restricted to results for:
1) Parental exposure
2) Exposure during child's lifetime (also including parent ever smoker, but not specific in utero exposure or specific discontinued exposure)
3) Results not by amount of exposure
4) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
5) ASTHMA : lifetime, current
6) WHOPAR : any/unspecified parent, mother regardless of father, mother only, father regardless of mother, father only
7) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
8) UNEXSO : not specific parent, neither parent, none in household
9) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
10) UNEXHI : not exposed defined as smoked none, or smoked none+low
11) RACE : all in study or nearest available, otherwise by race
12) ONSET : yes, no (prevalence)
13) For overlapping studies: principal rather than subsidiary studies, and for prospective studies, most recent follow-up

Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	108
NS	104
Wt	4622.32
Het Chi	168.96
Het df	107
Het P	***
Fixed RR	1.27
RRl	1.23
RRu	1.30
P	+++
Random RR	1.26
RRl	1.21
RRu	1.32
P	+++
Asymm P	N.S.

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N	99	5	4	24	17	67	5	11	31	47	14
Het P	***	N.S.	N.S.	*	(*)	**	N.S.	*	*	**	*
Fixed RR	1.27	1.34	1.18	1.28	1.27	1.26	1.23	1.22	1.34	1.23	1.28
RRl	1.23	1.09	0.93	1.18	1.21	1.21	1.08	1.12	1.26	1.17	1.21
RRu	1.30	1.64	1.50	1.39	1.33	1.31	1.41	1.33	1.43	1.30	1.34
P	+++	++	N.S.	+++	+++	+++	++	+++	+++	+++	+++
Between P	N.S.			N.S.			N.S.				

Table C26. Continued

	Publication year				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	16	26	30	36	27	4	48	21	6	2
Het P	**	*	N.S.	**	N.S.	N.S.	***	(*)	*	N.S.
Fixed RR	1.17	1.28	1.31	1.26	1.33	1.36	1.26	1.22	1.20	1.68
RRl	1.06	1.19	1.24	1.20	1.24	1.13	1.21	1.11	1.08	1.13
RRu	1.30	1.37	1.38	1.31	1.43	1.64	1.30	1.34	1.33	2.51
P	++	+++	+++	+++	+++	++	+++	+++	+++	+
Between P	N.S.				N.S.					

	Country in Europe						*Country in Asia*			*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	FarEast	Cent/SE	MidlEast	0-9	10-14	15+	unknown
N	15	5	3	14	8	3	10	1	10	27	37	42	2
Het P	**	N.S.	*	**	(*)	N.S.	N.S.	N.S.	N.S.	**	*	*	N.S.
Fixed RR	1.28	1.30	1.12	1.21	1.16	1.21	1.12	0.79	1.32	1.31	1.25	1.27	1.54
RRl	1.22	1.18	0.94	1.09	0.99	1.01	0.97	0.42	1.17	1.23	1.20	1.20	1.04
RRu	1.34	1.43	1.34	1.34	1.37	1.45	1.29	1.47	1.49	1.40	1.30	1.34	2.29
P	+++	+++	N.S.	+++	(+)	+	N.S.	N.S.	+++	+++	+++	+++	+
Between P	N.S.						(*)			N.S.			

	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	24	49	29	3	3	8	71	3	26	19	12	77	56	52
Het P	**	*	(*)	N.S.	N.S.	*	***	N.S.	N.S.	N.S.	N.S.	***	***	*
Fixed RR	1.21	1.27	1.32	1.19	1.13	1.10	1.26	1.31	1.29	1.18	1.29	1.27	1.28	1.25
RRl	1.13	1.21	1.25	0.92	0.96	0.98	1.21	1.24	1.20	1.08	1.19	1.23	1.23	1.20
RRu	1.29	1.32	1.38	1.53	1.33	1.23	1.31	1.38	1.38	1.30	1.40	1.32	1.34	1.30
P	+++	+++	+++	N.S.	N.S.	(+)	+++	+++	+++	+++	+++	+++	+++	+++
Between P	N.S.					(*)				N.S.			N.S.	

	Respondent for diagnosis				*Questionnaire for symptoms*			*Analysis type*		*Number of cases (lifetime/current asthma)*				
	medrec	parent	child	mixed	ISAAC	ATS	other	prevlnce	onset	1-50	51-100	101-200	201+	unknown
N	23	64	14	7	19	11	78	96	12	14	18	27	47	2
Het P	(*)	*	*	N.S.	N.S.	N.S.	***	***	(*)	N.S.	(*)	***	*	N.S.
Fixed RR	1.31	1.29	1.06	1.24	1.21	1.28	1.29	1.27	1.27	1.35	1.47	1.18	1.27	1.38
RRl	1.24	1.24	0.97	1.12	1.14	1.17	1.24	1.22	1.20	1.09	1.29	1.08	1.23	1.01
RRu	1.38	1.34	1.16	1.38	1.28	1.40	1.33	1.31	1.33	1.68	1.67	1.28	1.31	1.88
P	+++	+++	N.S.	+++	+++	+++	+++	+++	+++	++	+++	+++	+++	+
Between P	***				N.S.			N.S.		(*)				

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	56	52	38	70	13	95	27	81	34	74	35	73	17	91
Het P	**	**	**	**	N.S.	***	*	**	**	**	(*)	***	*	**
Fixed RR	1.26	1.27	1.24	1.28	1.33	1.26	1.23	1.28	1.24	1.28	1.25	1.27	1.23	1.27
RRl	1.21	1.22	1.17	1.23	1.23	1.22	1.16	1.24	1.18	1.23	1.19	1.23	1.15	1.23
RRu	1.32	1.32	1.31	1.32	1.44	1.30	1.30	1.33	1.31	1.32	1.31	1.32	1.32	1.32
P	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.		N.S.	

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*		*Asthma definition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	lifetime	current
N	13	95	17	91	15	93	32	76	7	101	27	81	71	37
Het P	N.S.	***	N.S.	***	N.S.	***	(*)	***	(*)	***	N.S.	***	**	**
Fixed RR	1.29	1.26	1.23	1.27	1.27	1.27	1.27	1.27	1.21	1.27	1.31	1.25	1.27	1.24
RRl	1.21	1.22	1.14	1.23	1.15	1.23	1.19	1.23	1.09	1.23	1.24	1.21	1.23	1.17
RRu	1.38	1.30	1.32	1.31	1.41	1.30	1.35	1.31	1.36	1.31	1.39	1.29	1.32	1.32
P	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.		N.S.	

	Exposed group : who is smoker			*Exposed group : when exposed*				
	AnyPar	Mother	Father	lif/ev	age<7y	current	unspec	other
N	41	60	7	31	9	29	37	2
Het P	N.S.	***	N.S.	**	***	(*)	(*)	(*)
Fixed RR	1.22	1.30	1.02	1.26	1.30	1.25	1.29	1.27
RRl	1.15	1.25	0.86	1.20	1.19	1.18	1.21	0.98
RRu	1.29	1.34	1.21	1.32	1.43	1.32	1.36	1.65
P	+++	+++	N.S.	+++	+++	+++	+++	(+)
Between P	**			N.S.				

Table C26. Continued

	Unexposed group : who is smoker			*Unexposed group : time*				*Number of adjustment variables*					
	NoHhMem	NoParent	NotSpPar	non	never	non+othr	NA	0	1	2	3-5	6-9	10+
N	6	42	60	90	18	0	0	53	13	3	15	18	6
Het P	N.S.	N.S.	***	***	*			*	*	N.S.	**	**	N.S.
Fixed RR	0.96	1.22	1.30	1.26	1.28			1.26	1.28	1.37	1.28	1.26	1.25
RRl	0.77	1.15	1.25	1.22	1.22			1.21	1.12	1.21	1.16	1.17	1.13
RRu	1.19	1.29	1.34	1.31	1.34			1.31	1.46	1.56	1.40	1.36	1.38
P	N.S.	+++	+++	+++	+++			+++	+++	+++	+++	+++	+++
Between P	**			N.S.				N.S.					

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	38	70	27	81	12	96	50	58	41	26	18	23
Het P	**	**	*	**	N.S.	***	***	*	*	N.S.	N.S.	***
Fixed RR	1.28	1.26	1.22	1.28	1.31	1.26	1.29	1.25	1.26	1.33	1.18	1.27
RRl	1.22	1.22	1.15	1.24	1.21	1.22	1.23	1.21	1.20	1.24	1.07	1.21
RRu	1.34	1.31	1.30	1.32	1.41	1.30	1.35	1.30	1.32	1.44	1.30	1.33
P	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Between P	N.S.		N.S.		N.S.		N.S.		N.S.			

Table C31. Children - Meta-analysis of Exposure during Lifetime, Biochemical/Total (or nearest equivalent), Physician Diagnosed Lifetime Asthma

This analysis is restricted to results for:
1) Physician diagnosed lifetime asthma
2) Biochemical, total, household (overall), or parental exposure
3) Exposure during child's lifetime (also including parent ever smoker, but not specific in utero exposure or specific discontinued exposure)
4) Results not by amount of exposure
5) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
6) EXPOS : biochemical, total, household, parent
7) BIOMEA : saliva, blood, urine
8) WHOPAR : any/unspecified parent, mother regardless of father, mother only, father regardless of mother, father only
9) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
10) UNEXSO : not specific parent, neither parent, none in household, none
11) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
12) UNEXHI : not exposed defined as smoked none, or smoked none+low
13) RACE : all in study or nearest available, otherwise by race
14) ONSET : yes, no (prevalence)
15) For overlapping studies: principal rather than subsidiary studies
Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	64
NS	60
Wt	4103.01
Het Chi	211.07
Het df	63
Het P	***
Fixed RR	1.18
RRl	1.14
RRu	1.22
P	+++
Random RR	1.21
RRl	1.13
RRu	1.30
P	+++
Asymm P	N.S.

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N	56	4	4	7	14	43	1	9	16	34	4
Het P	***	(*)	N.S.	(*)	*	***	N.S.	N.S.	N.S.	***	**
Fixed RR	1.19	1.11	1.05	1.42	1.27	1.12	1.29	1.17	1.31	1.11	1.25
RRl	1.15	0.94	0.88	1.15	1.21	1.08	0.92	1.03	1.18	1.07	1.19
RRu	1.22	1.31	1.25	1.74	1.33	1.17	1.80	1.32	1.44	1.16	1.32
P	+++	N.S.	N.S.	+++	+++	+++	N.S.	+	+++	+++	+++
Between P	N.S.			***			**				

Table C31. Continued

	Publication year				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	8	12	21	23	25	2	23	9	5	0
Het P	*	N.S.	*	***	***	N.S.	**	*	N.S.	
Fixed RR	1.15	1.19	1.19	1.18	1.31	1.27	1.27	0.89	1.09	
RRl	0.99	1.08	1.12	1.13	1.21	0.98	1.22	0.83	0.99	
RRu	1.33	1.31	1.26	1.22	1.41	1.63	1.33	0.96	1.20	
P	(+)	+++	+++	+++	+++	(+)	+++	--	(+)	
Between P	N.S.				***					

	Country in Europe						*Country in Asia*			*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	FarEast	Cent/SE	MidlEast	0-9	10-14	15+	unknown
N	6	1	7	2	4	3	7	1	1	15	23	25	1
Het P	**	N.S.	N.S.	N.S.	N.S.	N.S.	(*)	N.S.	N.S.	**	***	***	N.S.
Fixed RR	1.28	1.54	1.10	1.54	1.08	1.38	0.87	1.07	1.51	1.17	1.28	1.04	1.18
RRl	1.21	1.28	0.97	1.08	0.89	1.21	0.81	0.58	1.00	1.07	1.23	0.98	0.62
RRu	1.35	1.85	1.25	2.20	1.31	1.56	0.94	1.99	2.28	1.28	1.34	1.09	2.24
P	+++	+++	N.S.	+	N.S.	+++	---	N.S.	+	+++	+++	N.S.	N.S.
Between P	*						*			***			

	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	11	30	17	3	3	6	39	3	16	15	8	41	64	64
Het P	N.S.	***	N.S.	N.S.	N.S.	N.S.	***	N.S.	***	N.S.	(*)	***	***	***
Fixed RR	1.23	1.09	1.29	1.16	1.35	0.98	1.10	1.31	1.29	1.08	1.24	1.19	1.18	1.18
RRl	1.09	1.04	1.23	0.91	1.00	0.88	1.06	1.24	1.19	0.98	1.10	1.15	1.14	1.14
RRu	1.38	1.14	1.35	1.47	1.82	1.10	1.15	1.38	1.40	1.18	1.41	1.23	1.22	1.22
P	+++	+++	+++	N.S.	+	N.S.	+++	+++	+++	N.S.	+++	+++	+++	+++
Between P	***					***				N.S.			N.S.	

	Respondent for diagnosis				*Questionnaire for symptoms*			*Analysis type*		*Number of cases (lifetime asthma)*				
	medrec	parent	child	mixed	ISAAC	ATS	other	prevlnce	onset	1-50	51-100	101-200	201+	unknown
N	12	38	10	4	11	5	48	53	11	7	10	14	31	2
Het P	N.S.	***	*	(*)	***	N.S.	***	***	(*)	N.S.	N.S.	*	***	N.S.
Fixed RR	1.30	1.10	1.03	1.81	0.93	1.17	1.27	1.13	1.27	1.40	1.46	1.20	1.17	1.38
RRl	1.23	1.06	0.93	1.54	0.88	0.94	1.23	1.09	1.21	1.00	1.22	1.07	1.13	1.01
RRu	1.37	1.15	1.13	2.12	0.99	1.46	1.32	1.17	1.34	1.96	1.76	1.34	1.20	1.88
P	+++	+++	N.S.	+++	-	N.S.	+++	+++	+++	+	+++	++	+++	+
Between P	***				***			***		(*)				

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	29	35	18	46	12	52	13	51	20	44	20	44	11	53
Het P	**	***	N.S.	***	*	***	*	***	**	***	(*)	***	N.S.	***
Fixed RR	1.17	1.18	1.09	1.19	1.16	1.18	1.09	1.19	1.16	1.18	1.18	1.18	1.21	1.18
RRl	1.10	1.14	1.01	1.15	1.05	1.14	1.01	1.16	1.06	1.14	1.10	1.14	1.09	1.14
RRu	1.25	1.22	1.19	1.23	1.28	1.22	1.18	1.24	1.26	1.22	1.26	1.22	1.35	1.21
P	+++	+++	+	+++	++	+++	+	+++	+++	+++	+++	+++	+++	+++
Between P	N.S.		(*)		N.S.		*		N.S.		N.S.		N.S.	

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	9	55	9	55	7	57	21	43	4	60	10	54
Het P	N.S.	***	**	***	***	***	**	***	N.S.	***	*	***
Fixed RR	1.42	1.16	1.55	1.16	1.44	1.16	1.16	1.18	0.99	1.19	1.17	1.18
RRl	1.28	1.12	1.38	1.12	1.29	1.12	1.09	1.14	0.85	1.15	1.08	1.14
RRu	1.58	1.20	1.74	1.19	1.60	1.20	1.24	1.23	1.15	1.23	1.27	1.22
P	+++	+++	+++	+++	+++	+++	+++	+++	N.S.	+++	+++	+++
Between P	***		***		***		N.S.		*		N.S.	

	Exposed group : Source/who is smoker						*Exposed group : when exposed*				
	Biochem	TotETS	AnyHh	AnyPar	Mother	Father	lif/ev	age<7y	current	unspec	other
N	2	3	33	9	14	3	17	5	17	20	5
Het P	N.S.	N.S.	***	N.S.	*	N.S.	N.S.	***	**	***	(*)
Fixed RR	1.36	1.65	1.08	1.28	1.30	1.19	1.26	1.14	1.36	1.04	1.27
RRl	0.97	1.12	1.04	1.12	1.24	0.93	1.20	0.91	1.25	0.99	1.06
RRu	1.91	2.43	1.13	1.47	1.37	1.54	1.32	1.41	1.47	1.10	1.52
P	(+)	+	+++	+++	+++	N.S.	+++	N.S.	+++	(+)	++
Between P	***						***				

Table C31. Continued

	Unexposed group : who is smoker			*Unexposed group : time*				*Number of adjustment variables*					
	NoHhMem	NoParent	NotSpPar	non	never	non+othr	NA	0	1	2	3-5	6-9	10+
N	38	11	15	52	10	0	2	30	8	3	10	10	3
Het P	***	N.S.	*	***	N.S.		N.S.	***	**	*	*	N.S.	N.S.
Fixed RR	1.09	1.25	1.30	1.11	1.31		1.36	1.15	1.16	1.71	1.09	1.32	1.02
RRl	1.05	1.11	1.24	1.07	1.24		0.97	1.11	1.02	1.51	1.00	1.17	0.82
RRu	1.14	1.41	1.37	1.16	1.37		1.91	1.19	1.31	1.95	1.19	1.48	1.28
P	+++	+++	+++	+++	+++		(+)	+++	+	+++	(+)	+++	N.S.
Between P	***			***				***					

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	19	45	17	47	4	60	32	32	26	20	7	11
Het P	**	***	N.S.	***	N.S.	***	***	***	***	***	N.S.	***
Fixed RR	1.23	1.17	1.10	1.19	0.97	1.19	1.24	1.15	1.28	1.00	1.13	1.27
RRl	1.14	1.13	1.01	1.15	0.83	1.15	1.17	1.11	1.21	0.95	0.99	1.21
RRu	1.32	1.21	1.19	1.23	1.14	1.22	1.31	1.19	1.36	1.06	1.28	1.34
P	+++	+++	+	+++	N.S.	+++	+++	+++	+++	N.S.	(+)	+++
Between P	N.S.		(*)		*		*		***			

Table C33. Children - Meta-analysis of Exposure during Lifetime, Biochemical/Total (or nearest equivalent), Physician Diagnosed Current Asthma

This analysis is restricted to results for:
1) Physician diagnosed current asthma
2) Biochemical, total, household (overall), or parental exposure
3) Exposure during child's lifetime (also including parent ever smoker, but not specific in utero exposure or specific discontinued exposure)
4) Results not by amount of exposure
5) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
6) EXPOS : biochemical, total, household, parent
7) BIOMEA : saliva, blood, urine
8) WHOPAR : any/unspecified parent, mother regardless of father, mother only, father regardless of mother, father only
9) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
10) UNEXSO : not specific parent, neither parent, none in household, none
11) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
12) UNEXHI : not exposed defined as smoked none, or smoked none+low
13) RACE : all in study or nearest available, otherwise by race
14) For overlapping studies: principal rather than subsidiary studies, and for prospective studies, most recent follow-up

Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	32
NS	32
Wt	530.56
Het Chi	55.45
Het df	31
Het P	**
Fixed RR	1.19
RRl	1.09
RRu	1.30
P	+++
Random RR	1.23
RRl	1.08
RRu	1.39
P	++
Asymm P	N.S.

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N	32	0	0	16	4	12	0	1	6	19	6
Het P	**			N.S.	*	**		N.S.	*	*	N.S.
Fixed RR	1.19			1.34	1.08	1.10		0.35	1.21	1.18	1.29
RRl	1.09			1.17	0.86	0.97		0.08	1.01	1.06	1.00
RRu	1.30			1.54	1.35	1.25		1.47	1.44	1.31	1.67
P	+++			+++	N.S.	N.S.		N.S.	+	++	(+)
Between P	N.S.			(*)			N.S.				

Table C33. Continued

	Publication year				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	1	11	12	8	5	1	15	7	0	4
Het P	N.S.	N.S.	(*)	**	N.S.	N.S.	*	N.S.		N.S.
Fixed RR	0.35	1.31	1.18	1.11	1.43	1.22	1.22	0.94		1.77
RRl	0.08	1.11	1.05	0.94	1.10	0.31	1.09	0.80		1.27
RRu	1.47	1.55	1.34	1.32	1.84	4.83	1.37	1.12		2.47
P	N.S.	++	++	N.S.	++	N.S.	+++	N.S.		+++
Between P	N.S.				**					

	Country in Europe						*Country in Asia*			*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	FarEast	Cent/SE	MidlEast	0-9	10-14	15+	unknown
N	3	1	1	8	1	1	3	1	3	9	10	12	1
Het P	N.S.	N.S.	N.S.	**	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	*	N.S.
Fixed RR	1.48	1.00	1.32	1.17	2.07	1.28	0.85	1.13	1.04	1.54	1.12	1.07	1.96
RRl	0.88	0.70	0.88	1.01	1.21	0.94	0.68	0.82	0.69	1.27	0.99	0.91	1.10
RRu	2.48	1.42	1.97	1.36	3.54	1.75	1.06	1.57	1.57	1.87	1.26	1.26	3.48
P	N.S.	N.S.	N.S.	+	++	N.S.	N.S.	N.S.	N.S.	+++	(+)	N.S.	+
Between P	N.S.						N.S.			**			

	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	4	9	18	1	0	1	22	0	9	0	5	27	32	0
Het P	**	(*)	N.S.	N.S.		N.S.	**		N.S.		(*)	*	**	
Fixed RR	1.09	1.07	1.33	3.33		3.73	1.22		1.09		1.04	1.22	1.19	
RRl	0.91	0.92	1.17	0.78		1.17	1.10		0.91		0.84	1.11	1.09	
RRu	1.31	1.24	1.51	14.23		11.91	1.34		1.29		1.30	1.34	1.30	
P	N.S.	N.S.	+++	N.S.		+	+++		N.S.		N.S.	+++	+++	
Between P	*					(*)				N.S.			N.S.	

	Respondent for diagnosis				*Questionnaire for symptoms*			*Number of cases (current asthma)*				
	medrec	parent	child	mixed	ISAAC	ATS	other	1-50	51-100	101-200	201+	unknown
N	17	10	2	3	0	5	27	9	8	6	8	1
Het P	N.S.	(*)	N.S.	N.S.		*	*	N.S.	(*)	**	N.S.	N.S.
Fixed RR	1.33	1.25	0.80	1.05		1.22	1.18	1.57	1.25	1.10	1.17	1.32
RRl	1.16	1.09	0.62	0.84		1.01	1.08	1.13	1.00	0.93	1.03	0.88
RRu	1.52	1.44	1.04	1.31		1.47	1.30	2.16	1.55	1.30	1.32	1.97
P	+++	++	(-)	N.S.		+	+++	++	+	N.S.	+	N.S.
Between P	**				N.S.			N.S.				

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	20	12	21	11	0	32	14	18	10	22	11	21	4	28
Het P	**	(*)	**	N.S.		**	**	(*)	*	(*)	N.S.	**	*	*
Fixed RR	1.17	1.24	1.20	1.15		1.19	1.15	1.26	1.07	1.31	1.33	1.09	0.89	1.25
RRl	1.06	1.06	1.09	0.94		1.09	1.03	1.10	0.95	1.16	1.17	0.97	0.71	1.14
RRu	1.29	1.47	1.32	1.41		1.30	1.28	1.44	1.21	1.47	1.52	1.22	1.12	1.37
P	++	++	+++	N.S.		+++	+	+++	N.S.	+++	+++	N.S.	N.S.	+++
Between P	N.S.		N.S.		N.S.		N.S.		*		*		**	

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	8	24	9	23	8	24	11	21	0	32	9	23
Het P	*	*	(*)	*	(*)	*	N.S.	**		**	N.S.	*
Fixed RR	1.33	1.13	1.11	1.25	1.28	1.14	1.30	1.13		1.19	1.52	1.10
RRl	1.15	1.02	0.98	1.12	1.11	1.03	1.13	1.02		1.09	1.28	0.99
RRu	1.55	1.25	1.27	1.40	1.48	1.27	1.49	1.26		1.30	1.80	1.21
P	+++	+	N.S.	+++	+++	+	+++	+		+++	+++	(+)
Between P	(*)		N.S.		N.S.		N.S.		N.S.		**	

	Exposed group : Source/who is smoker						*Exposed group : when exposed*				
	Biochem	TotETS	AnyHh	AnyPar	Mother	Father	lif/ev	age<7y	current	unspec	other
N	1	1	14	7	7	2	5	5	6	15	1
Het P	N.S.	N.S.	(*)	N.S.	**	N.S.	*	N.S.	N.S.	*	N.S.
Fixed RR	1.88	1.13	1.15	1.39	1.16	1.01	1.00	1.40	1.05	1.23	1.88
RRl	0.60	0.82	1.02	1.14	0.95	0.69	0.81	1.18	0.87	1.07	0.60
RRu	5.88	1.57	1.30	1.69	1.42	1.48	1.23	1.67	1.26	1.42	5.88
P	N.S.	N.S.	+	++	N.S.	N.S.	N.S.	+++	N.S.	++	N.S.
Between P	N.S.						(*)				

Table C33. Continued

	Unexposed group : who is smoker			*Unexposed group : time*				*Number of adjustment variables*					
	NoHhMem	NoParent	NotSpPar	non	never	non+othr	NA	0	1	2	3-5	6-9	10+
N	18	7	7	28	2	1	1	16	2	0	2	7	5
Het P	(*)	N.S.	**	*	N.S.	N.S.	N.S.	N.S.	N.S.		N.S.	*	(*)
Fixed RR	1.15	1.39	1.14	1.24	0.80	2.36	1.88	1.26	1.24		2.14	1.04	1.22
RRl	1.03	1.14	0.95	1.13	0.62	0.91	0.60	1.08	0.85		1.34	0.90	1.03
RRu	1.29	1.69	1.37	1.36	1.04	6.11	5.88	1.46	1.82		3.41	1.20	1.45
P	+	++	N.S.	+++	(-)	(+)	N.S.	++	N.S.		++	N.S.	+
Between P	N.S.			**				*					

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	12	20	10	22	5	27	16	16	10	8	6	8
Het P	**	N.S.	**	N.S.	N.S.	**	**	N.S.	N.S.	N.S.	N.S.	***
Fixed RR	1.18	1.21	1.16	1.23	1.39	1.15	1.16	1.26	1.24	1.27	1.22	1.11
RRl	1.05	1.06	1.03	1.09	1.15	1.04	1.04	1.08	1.06	1.02	1.00	0.96
RRu	1.32	1.37	1.30	1.38	1.68	1.26	1.29	1.46	1.44	1.60	1.49	1.28
P	++	++	+	+++	+++	++	++	++	++	+	+	N.S.
Between P	N.S.		N.S.		(*)		N.S.		N.S.			

Table C41. Children - Meta-analysis of Parental Exposure during Lifetime, Both Parents specifically, Lifetime Asthma

This analysis is restricted to results for:
1) Lifetime asthma
2) Parental exposure (both parents)
3) Exposure during child's lifetime (also including parent ever smoker, but not specific in utero exposure or specific discontinued exposure)
4) Results not by amount of exposure
5) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
6) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
7) UNEXSO : neither parent, none in household
8) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
9) UNEXHI : not exposed defined as smoked none, or smoked none+low
10) RACE : all in study or nearest available, otherwise by race
11) ONSET : yes, no (prevalence)
12) For overlapping studies: principal rather than subsidiary studies

Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	9
NS	8
Wt	260.40
Het Chi	12.95
Het df	8
Het P	N.S.
Fixed RR	1.40
RRl	1.24
RRu	1.58
P	+++
Random RR	1.44
RRl	1.22
RRu	1.70
P	+++
Asymm P	N.S.

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N	7	1	1	0	3	6	2	2	4	0	1
Het P	(*)	N.S.	N.S.		*	N.S.	N.S.	N.S.	(*)		N.S.
Fixed RR	1.38	1.72	1.24		1.48	1.38	1.50	1.19	1.36		1.93
RRl	1.20	1.20	0.81		1.09	1.21	1.14	0.84	1.16		1.23
RRu	1.57	2.47	1.89		2.01	1.58	1.97	1.70	1.58		3.02
P	+++	++	N.S.		+	+++	++	N.S.	+++		++
Between P	N.S.			N.S.			N.S.				

Table C41. Continued

	Publication year				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	4	2	3	0	4	0	3	1	1	0
Het P	N.S.	N.S.	*		N.S.		N.S.	N.S.	N.S.	
Fixed RR	1.37	1.25	1.51		1.67		1.38	1.32	1.10	
RRl	1.11	0.99	1.26		1.31		1.12	1.07	0.75	
RRu	1.71	1.59	1.82		2.13		1.70	1.64	1.63	
P	++	(+)	+++		+++		++	+	N.S.	
Between P	N.S.				N.S.					

	Country in Europe						*Country in Asia*			*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	FarEast	Cent/SE	MidlEast	0-9	10-14	15+	unknown
N	1	1	1	0	0	0	0	0	1	1	5	3	0
Het P	N.S.	N.S.	N.S.						N.S.	N.S.	N.S.	(*)	
Fixed RR	1.93	1.50	1.11						1.32	1.10	1.36	1.67	
RRl	1.23	1.03	0.82						1.07	0.75	1.17	1.30	
RRu	3.02	2.18	1.51						1.64	1.63	1.58	2.15	
P	++	+	N.S.						+	N.S.	+++	+++	
Between P	N.S.						N.S.			N.S.			

	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	2	5	2	0	0	0	6	0	3	3	1	5	4	5
Het P	N.S.	(*)	(*)				N.S.		(*)	N.S.	N.S.	N.S.	*	N.S.
Fixed RR	1.50	1.37	1.40				1.33		1.67	1.52	2.90	1.32	1.28	1.45
RRl	1.14	1.17	1.05				1.15		1.30	1.17	1.55	1.14	1.03	1.26
RRu	1.97	1.59	1.88				1.52		2.15	1.97	5.43	1.51	1.59	1.68
P	++	+++	+				+++		+++	++	+++	+++	+	+++
Between P	N.S.					N.S.				*			N.S.	

	Respondent for diagnosis				*Questionnaire for symptoms*			*Analysis type*		*Number of cases (lifetime asthma)*				
	medrec	parent	child	mixed	ISAAC	ATS	other	prevlnce	onset	1-50	51-100	101-200	201+	unknown
N	1	7	1	0	0	2	7	8	1	1	1	7		0
Het P	N.S.	N.S.	N.S.			N.S.	(*)	N.S.	N.S.	N.S.	N.S.	(*)		
Fixed RR	1.10	1.39	2.90			1.36	1.42	1.43	1.10	1.73	1.10	1.43		
RRl	0.75	1.22	1.55			1.13	1.21	1.26	0.75	0.74	0.75	1.25		
RRu	1.63	1.58	5.43			1.65	1.67	1.63	1.63	4.04	1.63	1.62		
P	N.S.	+++	+++			++	+++	+++	N.S.	N.S.	N.S.	+++		
Between P	*				N.S.			N.S.		N.S.				

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	3	6	3	6	2	7	2	7	3	6	2	7	2	7
Het P	*	N.S.	N.S.	*	N.S.	N.S.	N.S.	(*)	*	N.S.	N.S.	N.S.	N.S.	(*)
Fixed RR	1.47	1.38	1.50	1.36	2.42	1.35	1.36	1.42	1.47	1.38	1.27	1.50	1.29	1.43
RRl	1.15	1.20	1.20	1.17	1.46	1.19	1.13	1.21	1.15	1.20	1.05	1.28	0.99	1.24
RRu	1.88	1.58	1.87	1.57	4.00	1.53	1.65	1.67	1.88	1.58	1.53	1.75	1.70	1.63
P	++	+++	+++	+++	+++	+++	++	+++	++	+++	+	+++	(+)	+++
Between P	N.S.		N.S.		*		N.S.		N.S.		N.S.		N.S.	

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	1	8	1	8	1	8	5	4	0	9	5	4
Het P	N.S.	(*)	N.S.	(*)	N.S.	N.S.	N.S.	N.S.		N.S.	N.S.	N.S.
Fixed RR	1.50	1.39	1.50	1.39	1.10	1.43	1.34	1.46		1.40	1.32	1.67
RRl	1.03	1.22	1.03	1.22	0.75	1.26	1.13	1.23		1.24	1.14	1.31
RRu	2.18	1.58	2.18	1.58	1.63	1.63	1.59	1.74		1.58	1.51	2.13
P	+	+++	+	+++	N.S.	+++	+++	+++		+++	+++	+++
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		(*)	

	Exposed group : when exposed				
	lif/ev	age<7y	current	unspec	other
N	4	0	0	4	1
Het P	N.S.			N.S.	N.S.
Fixed RR	1.34			1.40	2.90
RRl	1.14			1.14	1.55
RRu	1.56			1.71	5.43
P	+++			++	+++
Between P	(*)				

Table C41. Continued

	Unexposed group : who is smoker			*Unexposed group : time*				*Number of adjustment variables*					
	NoHhMem	NoParent	NotSpPar	non	never	non+othr	NA	0	1	2	3-5	6-9	10+
N	0	9	0	8	1	0	0	3	4	0	1	1	0
Het P		N.S.		(*)	N.S.			N.S.	N.S.		N.S.	N.S.	
Fixed RR		1.40		1.43	1.32			1.22	1.61		2.90	1.50	
RRl		1.24		1.24	1.07			1.04	1.29		1.55	1.03	
RRu		1.58		1.66	1.64			1.44	2.02		5.43	2.18	
P		+++		+++	+			+	+++		+++	+	
Between P	N.S.			N.S.				*					

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	2	7	3	6	0	9	4	5	2	3	2	2
Het P	(*)	N.S.	N.S.	*		N.S.	N.S.	N.S.	(*)	N.S.	(*)	N.S.
Fixed RR	1.78	1.34	1.50	1.36		1.40	1.82	1.29	1.78	1.27	1.40	1.50
RRl	1.29	1.18	1.20	1.17		1.24	1.42	1.12	1.29	1.06	1.05	1.14
RRu	2.46	1.53	1.87	1.57		1.58	2.34	1.48	2.46	1.51	1.88	1.97
P	+++	+++	+++	+++		+++	+++	+++	+++	++	+	++
Between P	N.S.		N.S.		N.S.		*		N.S.			

Table C43. Children - Meta-analysis of Parental Exposure during Lifetime, Both Parents specifically, Current Asthma

This analysis is restricted to results for:
1) Current asthma
2) Parental exposure (both parents)
3) Exposure during child's lifetime (also including parent ever smoker, but not specific in utero exposure or specific discontinued exposure)
4) Results not by amount of exposure
5) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
6) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
7) UNEXSO : neither parent, none in household
8) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
9) UNEXHI : not exposed defined as smoked none, or smoked none+low
10) RACE : all in study or nearest available, otherwise by race
11) For overlapping studies: principal rather than subsidiary studies, and for prospective studies, most recent follow-up

Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	7
NS	7
Wt	216.14
Het Chi	15.52
Het df	6
Het P	*
Fixed RR	1.41
RRl	1.24
RRu	1.61
P	+++
Random RR	1.69
RRl	1.25
RRu	2.27
P	+++
Asymm P	*

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N	7	0	0	4	2	1	0	0	2	5	0
Het P	*			N.S.	N.S.	N.S.			N.S.	(*)	
Fixed RR	1.41			1.33	4.04	1.40			2.79	1.35	
RRl	1.24			1.16	2.20	0.88			1.61	1.18	
RRu	1.61			1.54	7.39	2.24			4.82	1.55	
P	+++			+++	+++	N.S.			+++	+++	
Between P	N.S.			**			*				

Table C43. Continued

	Publication year				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	0	2	3	2	2	0	4	0	0	1
Het P		(*)	*	N.S.	*		*			N.S.
Fixed RR		3.27	1.37	1.46	1.86		1.35			2.48
RRl		1.45	1.19	0.93	1.27		1.17			0.44
RRu		7.34	1.58	2.29	2.73		1.56			13.96
P		++	+++	N.S.	++		+++			N.S.
Between P	N.S.				N.S.					

	Country in Europe						*Country in Asia*			*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	FarEast	Cent/SE	MidlEast	0-9	10-14	15+	unknown
N	1	2	0	1	0	0	0	0	0	3	1	3	0
Het P	N.S.	N.S.		N.S.						*	N.S.	N.S.	
Fixed RR	11.00	1.32		1.94						1.42	1.29	1.87	
RRl	2.51	1.14		0.74						1.15	1.06	1.31	
RRu	48.30	1.52		5.12						1.77	1.56	2.68	
P	++	+++		N.S.						++	++	+++	
Between P	*									N.S.			

	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	0	4	2	1	0	0	5	0	2	2	2	3	3	4
Het P		(*)	N.S.	N.S.			(*)		*	N.S.	**	N.S.	N.S.	(*)
Fixed RR		1.37	2.06	11.00			1.36		1.86	1.36	1.39	3.11	3.11	1.37
RRl		1.20	0.89	2.51			1.18		1.27	1.11	1.15	1.49	1.49	1.20
RRu		1.57	4.79	48.30			1.57		2.73	1.66	1.67	6.47	6.47	1.57
P		+++	(+)	++			+++		++	++	+++	++	++	+++
Between P	*					N.S.				(*)			*	

	Respondent for diagnosis				*Questionnaire for symptoms*			*Number of cases (current asthma)*				
	medrec	parent	child	mixed	ISAAC	ATS	other	1-50	51-100	101-200	201+	unknown
N	3	3	1	0	2	5		2	1	1	3	0
Het P	N.S.	N.S.	N.S.		N.S.	*		(*)	N.S.	N.S.	N.S.	
Fixed RR	3.11	1.32	3.30		1.32	2.08		3.27	2.48	3.30	1.32	
RRl	1.49	1.15	1.70		1.14	1.48		1.45	0.44	1.70	1.15	
RRu	6.47	1.52	6.40		1.52	2.92		7.34	13.96	6.40	1.52	
P	++	+++	+++		+++	+++		++	N.S.	+++	+++	
Between P	**				*			**				

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	5	2	4	3	2	5	3	4	4	3	4	3	0	7
Het P	**	N.S.	N.S.	N.S.	*	(*)	N.S.	N.S.	**	N.S.	*	N.S.		*
Fixed RR	1.40	2.06	1.33	3.29	1.86	1.36	1.32	3.21	1.40	1.53	1.35	2.76		1.41
RRl	1.22	0.89	1.16	1.97	1.27	1.18	1.15	1.96	1.21	1.02	1.17	1.64		1.24
RRu	1.60	4.79	1.52	5.49	2.73	1.57	1.52	5.25	1.61	2.31	1.55	4.64		1.61
P	+++	(+)	+++	+++	++	+++	+++	+++	+++	+	+++	+++		+++
Between P	N.S.		***		N.S.		***		N.S.		**		N.S.	

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	2	5	2	5	1	6	2	5	3	4	6	1
Het P	N.S.	*	N.S.	*	N.S.	N.S.	**	(*)	N.S.	N.S.	N.S.	N.S.
Fixed RR	1.32	2.08	1.32	2.08	11.00	1.39	1.69	1.39	1.32	3.21	1.36	3.30
RRl	1.14	1.48	1.14	1.48	2.51	1.21	1.08	1.21	1.15	1.96	1.19	1.70
RRu	1.52	2.92	1.52	2.92	48.30	1.59	2.64	1.60	1.52	5.25	1.56	6.40
P	+++	+++	+++	+++	++	+++	+	+++	+++	+++	+++	+++
Between P	*		*		**		N.S.		***		*	

	Exposed group : when exposed				
	lif/ev	age<7y	current	unspec	other
N	1	4	1	1	0
Het P	N.S.	N.S.	N.S.	N.S.	
Fixed RR	11.00	1.33	2.48	3.30	
RRl	2.51	1.16	0.44	1.70	
RRu	48.30	1.53	13.96	6.40	
P	++	+++	N.S.	+++	
Between P	**				

Table C43. Continued

	Unexposed group : who is smoker			*Unexposed group : time*				*Number of adjustment variables*					
	NoHhMem	NoParent	NotSpPar	non	never	non+othr	NA	0	1	2	3-5	6-9	10+
N	1	6	0	5	2	0	0	2	0	0	1	2	2
Het P	N.S.	**		*	N.S.			N.S.			N.S.	**	N.S.
Fixed RR	1.40	1.41		2.08	1.32			2.06			3.30	1.69	1.32
RRl	0.88	1.23		1.48	1.14			0.89			1.70	1.08	1.14
RRu	2.24	1.62		2.92	1.52			4.79			6.40	2.64	1.52
P	N.S.	+++		+++	+++			(+)			+++	+	+++
Between P	N.S.			*				*					

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	5	2	3	4	2	5	5	2	5	1	1	0
Het P	**	N.S.	N.S.	N.S.	N.S.	*	**	N.S.	**	N.S.	N.S.	
Fixed RR	1.40	2.06	1.32	3.21	1.32	2.08	1.40	2.06	1.40	1.94	2.48	
RRl	1.22	0.89	1.15	1.96	1.14	1.48	1.22	0.89	1.22	0.74	0.44	
RRu	1.60	4.79	1.52	5.25	1.52	2.92	1.60	4.79	1.60	5.12	13.96	
P	+++	(+)	+++	+++	+++	+++	+++	(+)	+++	N.S.	N.S.	
Between P	N.S.		***		*		N.S.		N.S.			

Table C45. Children - Meta-analysis of Maternal Exposure during Lifetime, Lifetime Asthma

This analysis is restricted to results for:
1) Lifetime asthma
2) Maternal exposure
3) Exposure during child's lifetime (also including parent ever smoker, but not specific in utero exposure or specific discontinued exposure)
4) Results not by amount of exposure
5) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
6) WHOPAR : mother regardless of father, mother only
7) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
8) UNEXSO : not mother, neither parent, none in household
9) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
10) UNEXHI : not exposed defined as smoked none, or smoked none+low
11) RACE : all in study or nearest available, otherwise by race
12) ONSET : yes, no (prevalence)
13) For overlapping studies: principal rather than subsidiary studies

Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	49
NS	47
Wt	3072.48
Het Chi	88.85
Het df	48
Het P	***
Fixed RR	1.30
RRl	1.25
RRu	1.35
P	+++
Random RR	1.31
RRl	1.24
RRu	1.40
P	+++
Asymm P	N.S.

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N	44	3	2	4	12	33	1	9	16	16	7
Het P	***	N.S.	N.S.	N.S.	**	*	N.S.	**	*	(*)	(*)
Fixed RR	1.29	1.68	1.54	1.84	1.27	1.32	1.26	1.20	1.37	1.33	1.30
RRl	1.25	1.20	0.91	1.37	1.21	1.25	1.05	1.10	1.27	1.22	1.23
RRu	1.34	2.35	2.60	2.48	1.33	1.39	1.51	1.32	1.49	1.44	1.37
P	+++	++	N.S.	+++	+++	+++	+	+++	+++	+++	+++
Between P	N.S.			*			N.S.				

Table C45. Continued

	Publication year				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	8	12	15	14	15	1	22	6	5	0
Het P	***	N.S.	N.S.	*	N.S.	N.S.	***	N.S.	**	
Fixed RR	1.18	1.30	1.36	1.29	1.36	1.57	1.30	1.37	1.16	
RRl	1.02	1.19	1.26	1.23	1.25	0.53	1.25	1.18	1.04	
RRu	1.35	1.41	1.47	1.36	1.49	4.66	1.36	1.59	1.29	
P	+	+++	+++	+++	+++	N.S.	+++	+++	++	
Between P	N.S.				N.S.					

	Country in Europe						*Country in Asia*			*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	FarEast	Cent/SE	MidlEast	0-9	10-14	15+	unknown
N	8	2	2	5	3	2	1	0	5	11	19	19	0
Het P	**	N.S.	*	N.S.	N.S.	N.S.	N.S.		N.S.	***	*	N.S.	
Fixed RR	1.29	1.55	1.07	1.57	1.17	1.21	1.32		1.38	1.27	1.29	1.35	
RRl	1.22	1.33	0.87	1.32	0.91	0.99	0.71		1.18	1.17	1.23	1.25	
RRu	1.35	1.81	1.31	1.86	1.49	1.47	2.45		1.60	1.39	1.35	1.45	
P	+++	+++	N.S.	+++	N.S.	(+)	N.S.		+++	+++	+++	+++	
Between P	*						N.S.			N.S.			

	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	10	25	12	0	2	5	30	2	12	9	8	32	25	24
Het P	**	*	*		(*)	(*)	***	N.S.	N.S.	N.S.	N.S.	***	**	*
Fixed RR	1.26	1.31	1.32		1.14	1.06	1.31	1.31	1.33	1.31	1.32	1.30	1.31	1.29
RRl	1.14	1.24	1.25		0.96	0.91	1.24	1.24	1.22	1.09	1.20	1.25	1.25	1.22
RRu	1.39	1.39	1.39		1.35	1.24	1.39	1.39	1.46	1.57	1.46	1.35	1.37	1.36
P	+++	+++	+++		N.S.	N.S.	+++	+++	+++	++	+++	+++	+++	+++
Between P	N.S.					(*)				N.S.			N.S.	

	Respondent for diagnosis				*Questionnaire for symptoms*			*Analysis type*		*Number of cases (lifetime asthma)*				
	medrec	parent	child	mixed	ISAAC	ATS	other	prevlnce	onset	1-50	51-100	101-200	201+	unknown
N	6	29	8	6	10	7	32	39	10	3	8	11	25	2
Het P	**	*	*	N.S.	N.S.	N.S.	***	**	**	*	N.S.	**	*	N.S.
Fixed RR	1.30	1.34	1.09	1.27	1.16	1.33	1.33	1.33	1.26	1.19	1.70	1.26	1.29	1.38
RRl	1.23	1.27	0.96	1.14	1.06	1.21	1.28	1.27	1.20	0.72	1.39	1.10	1.24	1.01
RRu	1.38	1.42	1.24	1.42	1.26	1.46	1.39	1.40	1.33	1.96	2.08	1.44	1.34	1.88
P	+++	+++	N.S.	+++	+++	+++	+++	+++	+++	N.S.	+++	+++	+++	+
Between P	*				*			N.S.		N.S.				

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	25	24	12	37	7	42	7	42	15	34	19	30	9	40
Het P	*	***	N.S.	***	N.S.	***	N.S.	***	***	*	*	**	**	**
Fixed RR	1.33	1.29	1.34	1.29	1.33	1.30	1.30	1.30	1.27	1.31	1.25	1.32	1.27	1.31
RRl	1.25	1.23	1.23	1.24	1.20	1.25	1.19	1.25	1.18	1.26	1.17	1.27	1.17	1.26
RRu	1.41	1.34	1.46	1.34	1.48	1.34	1.42	1.35	1.37	1.36	1.33	1.38	1.38	1.36
P	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.		N.S.	

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	5	44	7	42	8	41	18	31	2	47	14	35
Het P	*	***	N.S.	***	(*)	***	**	**	**	***	*	**
Fixed RR	1.30	1.30	1.36	1.29	1.29	1.30	1.26	1.31	1.22	1.30	1.35	1.29
RRl	1.19	1.25	1.21	1.25	1.13	1.25	1.17	1.26	0.78	1.25	1.25	1.23
RRu	1.41	1.35	1.53	1.34	1.47	1.35	1.36	1.36	1.91	1.35	1.45	1.34
P	+++	+++	+++	+++	+++	+++	+++	+++	N.S.	+++	+++	+++
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.	

	Exposed group : who is smoker		*Exposed group : when exposed*				
	Mother	Mother only	lif/ev	age<7y	current	unspec	other
N	49	0	14	7	12	14	2
Het P	***		*	***	(*)	N.S.	(*)
Fixed RR	1.30		1.29	1.27	1.31	1.33	1.28
RRl	1.25		1.23	1.15	1.20	1.23	0.98
RRu	1.35		1.36	1.40	1.43	1.44	1.67
P	+++		+++	+++	+++	+++	(+)
Between P	N.S.		N.S.				

Table C45. Continued

	Unexposed group : who is smoker			*Unexposed group : time*				*Number of adjustment variables*					
	NoHhMem	NoParent	NotSpPar	non	never	non+othr	NA	0	1	2	3-5	6-9	10+
N	2	0	47	40	9	0	0	19	8	4	7	9	2
Het P	N.S.		***	***	N.S.			*	***	N.S.	N.S.	(*)	N.S.
Fixed RR	1.20		1.30	1.28	1.32			1.28	1.20	1.37	1.46	1.30	1.34
RRl	0.78		1.25	1.22	1.25			1.23	1.04	1.21	1.26	1.19	1.10
RRu	1.84		1.35	1.35	1.39			1.34	1.39	1.54	1.69	1.43	1.64
P	N.S.		+++	+++	+++			+++	+	+++	+++	+++	++
Between P	N.S.			N.S.				N.S.					

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	18	31	10	39	9	40	26	23	23	14	4	8
Het P	(*)	***	N.S.	***	*	**	**	**	*	N.S.	**	*
Fixed RR	1.35	1.28	1.39	1.29	1.31	1.30	1.36	1.27	1.28	1.34	1.05	1.32
RRl	1.26	1.23	1.23	1.24	1.17	1.25	1.28	1.22	1.20	1.23	0.85	1.25
RRu	1.45	1.34	1.56	1.34	1.47	1.35	1.44	1.33	1.35	1.47	1.30	1.39
P	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	N.S.	+++
Between P	N.S.		N.S.		N.S.		(*)		N.S.			

Table C47. Children - Meta-analysis of Maternal Exposure during Lifetime, Current Asthma

This analysis is restricted to results for:
1) Current asthma
2) Maternal exposure
3) Exposure during child's lifetime (also including parent ever smoker, but not specific in utero exposure or specific discontinued exposure)
4) Results not by amount of exposure
5) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
6) WHOPAR : mother regardless of father, mother only
7) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
8) UNEXSO : not mother, neither parent, none in household
9) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
10) UNEXHI : not exposed defined as smoked none, or smoked none+low
11) RACE : all in study or nearest available, otherwise by race
12) For overlapping studies: principal rather than subsidiary studies, and for prospective studies, most recent follow-up

Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	29
NS	29
Wt	1112.14
Het Chi	63.01
Het df	28
Het P	***
Fixed RR	1.21
RRl	1.14
RRu	1.29
P	+++
Random RR	1.25
RRl	1.12
RRu	1.40
P	+++
Asymm P	N.S.

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N	29	0	0	11	4	14	0	3	10	16	0
Het P	***			*	(*)	**		(*)	*	(*)	
Fixed RR	1.21			1.23	1.06	1.25		0.95	1.42	1.19	
RRl	1.14			1.14	0.91	1.13		0.80	1.26	1.11	
RRu	1.29			1.34	1.23	1.38		1.13	1.60	1.28	
P	+++			+++	N.S.	+++		N.S.	+++	+++	
Between P	N.S.			N.S.			***				

Table C47. Continued

	Publication year				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	3	8	11	7	9	1	11	6	1	1
Het P	(*)	***	N.S.	*	N.S.	N.S.	**	*	N.S.	N.S.
Fixed RR	0.77	1.26	1.24	1.05	1.20	1.53	1.20	1.24	0.36	2.44
RRl	0.48	1.10	1.16	0.89	1.08	1.14	1.11	0.99	0.13	0.61
RRu	1.24	1.43	1.34	1.24	1.33	2.04	1.30	1.55	1.00	9.74
P	N.S.	+++	+++	N.S.	+++	++	+++	(+)	(-)	N.S.
Between P	(*)				N.S.					

	Country in Europe						*Country in Asia*			*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	FarEast	Cent/SE	MidlEast	0-9	10-14	15+	unknown
N	4	2	0	3	2	0	3	0	3	7	6	15	1
Het P	N.S.	(*)		***	N.S.		(*)		(*)	N.S.	N.S.	***	N.S.
Fixed RR	1.15	1.19		1.14	2.27		1.55		1.19	1.31	1.10	1.29	1.96
RRl	0.89	1.09		0.91	1.41		0.87		0.93	1.17	1.00	1.15	1.10
RRu	1.47	1.30		1.44	3.67		2.77		1.51	1.47	1.20	1.44	3.48
P	N.S.	+++		N.S.	+++		N.S.		N.S.	+++	+	+++	+
Between P	(*)						N.S.			*			

	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	4	17	7	1	0	4	16	0	9	5	7	17	12	17
Het P	**	*	*	N.S.		*	**		*	*	N.S.	**	***	*
Fixed RR	1.14	1.21	1.49	2.02		1.22	1.22		1.19	1.27	1.11	1.29	1.23	1.21
RRl	0.99	1.13	1.15	0.82		0.97	1.13		1.07	1.12	1.01	1.17	1.04	1.14
RRu	1.32	1.29	1.93	4.99		1.53	1.31		1.33	1.45	1.22	1.42	1.47	1.29
P	(+)	+++	++	N.S.		(+)	+++		++	+++	+	+++	+	+++
Between P	N.S.					N.S.				(*)			N.S.	

	Respondent for diagnosis				*Questionnaire for symptoms*			*Number of cases (current asthma)*				
	medrec	parent	child	mixed	ISAAC	ATS	other	1-50	51-100	101-200	201+	unknown
N	9	13	7	0	8	2	19	4	7	5	12	1
Het P	(*)	*	**		N.S.	N.S.	***	*	N.S.	**	*	N.S.
Fixed RR	1.53	1.21	1.10		1.22	1.00	1.28	1.33	1.30	1.17	1.20	3.27
RRl	1.20	1.13	0.93		1.13	0.85	1.16	0.91	1.01	0.97	1.13	1.13
RRu	1.96	1.29	1.29		1.32	1.18	1.43	1.94	1.67	1.40	1.29	9.48
P	+++	+++	N.S.		+++	N.S.	+++	N.S.	+	(+)	+++	+
Between P	(*)				*			N.S.				

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	23	6	18	11	7	22	12	17	13	16	12	17	5	24
Het P	**	*	**	*	(*)	***	**	*	**	*	(*)	***	**	**
Fixed RR	1.20	1.39	1.19	1.30	1.18	1.23	1.18	1.40	1.18	1.38	1.18	1.29	1.11	1.26
RRl	1.13	1.10	1.11	1.14	1.07	1.14	1.10	1.22	1.11	1.19	1.10	1.16	1.01	1.17
RRu	1.28	1.75	1.27	1.49	1.31	1.32	1.25	1.61	1.26	1.59	1.27	1.44	1.24	1.36
P	+++	++	+++	+++	++	+++	+++	+++	+++	+++	+++	+++	+	+++
Between P	N.S.		N.S.		N.S.		*		(*)		N.S.		(*)	

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	7	22	7	22	6	23	7	22	5	24	13	16
Het P	*	***	N.S.	***	N.S.	***	N.S.	***	N.S.	***	(*)	***
Fixed RR	1.18	1.26	1.22	1.20	1.33	1.19	1.26	1.21	1.17	1.25	1.24	1.16
RRl	1.10	1.14	1.13	1.10	1.13	1.12	1.03	1.13	1.07	1.16	1.15	1.04
RRu	1.28	1.38	1.32	1.32	1.55	1.27	1.54	1.28	1.27	1.36	1.33	1.28
P	+++	+++	+++	+++	+++	+++	+	+++	+++	+++	+++	++
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.	

	Exposed group : who is smoker		*Exposed group : when exposed*				
	Mother	Mother only	lif/ev	age<7y	current	unspec	other
N	28	1	9	0	7	12	1
Het P	***	N.S.	**		*	(*)	N.S.
Fixed RR	1.22	0.90	1.13		1.32	1.40	1.60
RRl	1.15	0.52	1.05		1.16	1.19	1.03
RRu	1.29	1.56	1.22		1.50	1.64	2.48
P	+++	N.S.	+++		+++	+++	+
Between P	N.S.		*				

Table C47. Continued

	Unexposed group : who is smoker			*Unexposed group : time*				*Number of adjustment variables*					
	NoHhMem	NoParent	NotSpPar	non	never	non+othr	NA	0	1	2	3-5	6-9	10+
N	3	0	26	23	6	0	0	11	4	0	5	4	5
Het P	N.S.		***	*	**			*	(*)		N.S.	**	N.S.
Fixed RR	0.95		1.22	1.35	1.12			1.32	1.20		1.59	1.20	1.16
RRl	0.60		1.15	1.23	1.04			1.10	0.89		1.27	1.04	1.08
RRu	1.52		1.29	1.48	1.21			1.58	1.62		1.98	1.39	1.25
P	N.S.		+++	+++	++			++	N.S.		+++	+	+++
Between P	N.S.			**				(*)					

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	14	15	12	17	9	20	14	15	7	7	4	11
Het P	**	*	***	*	(*)	***	**	**	N.S.	N.S.	N.S.	***
Fixed RR	1.20	1.29	1.19	1.30	1.24	1.17	1.19	1.33	1.36	1.45	0.94	1.16
RRl	1.13	1.10	1.11	1.15	1.15	1.06	1.12	1.14	1.19	1.19	0.69	1.07
RRu	1.28	1.50	1.27	1.47	1.33	1.29	1.27	1.57	1.54	1.77	1.28	1.24
P	+++	++	+++	+++	+++	++	+++	+++	+++	+++	N.S.	+++
Between P	N.S.		N.S.		N.S.		N.S.		*			

Table C53. Children - Meta-analysis of Paternal Exposure during Lifetime, Lifetime Asthma

This analysis is restricted to results for:
1) Lifetime asthma
2) Paternal exposure
3) Exposure during child's lifetime (also including parent ever smoker, but not specific in utero exposure or specific discontinued exposure)
4) Results not by amount of exposure
5) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
6) WHOPAR : father regardless of mother, father only
7) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
8) UNEXSO : not father, neither parent, none in household
9) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
10) UNEXHI : not exposed defined as smoked none, or smoked none+low
11) RACE : all in study or nearest available, otherwise by race
12) ONSET : yes, no (prevalence)
13) For overlapping studies: principal rather than subsidiary studies

Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	35
NS	31
Wt	2415.51
Het Chi	69.17
Het df	34
Het P	***
Fixed RR	1.18
RRl	1.13
RRu	1.22
P	+++
Random RR	1.16
RRl	1.09
RRu	1.25
P	+++
Asymm P	N.S.

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N	26	5	4	1	6	28	2	5	11	11	6
Het P	*	***	N.S.	N.S.	N.S.	***	N.S.	N.S.	(*)	N.S.	***
Fixed RR	1.17	1.22	1.15	0.79	1.28	1.13	1.08	1.34	1.09	1.07	1.29
RRl	1.12	1.08	0.98	0.42	1.19	1.08	0.96	1.10	1.00	0.98	1.21
RRu	1.23	1.38	1.34	1.47	1.37	1.19	1.22	1.63	1.20	1.16	1.37
P	+++	++	(+)	N.S.	+++	+++	N.S.	++	(+)	N.S.	+++
Between P	N.S.			**			***				

Table C53. Continued

	Publication year				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	3	10	11	11	9	0	12	10	4	0
Het P	N.S.	N.S.	(*)	**	N.S.		N.S.	***	*	
Fixed RR	1.41	1.10	1.07	1.25	1.25		1.20	1.19	1.05	
RRl	1.12	1.00	0.99	1.18	1.06		1.14	1.09	0.95	
RRu	1.78	1.20	1.17	1.32	1.47		1.26	1.31	1.16	
P	++	+	(+)	+++	++		+++	+++	N.S.	
Between P	**				(*)					

	Country in Europe						*Country in Asia*			*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	FarEast	Cent/SE	MidlEast	0-9	10-14	15+	unknown
N	5	2	1	1	1	2	5	1	4	6	14	15	0
Het P	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	***	(*)	N.S.	**	
Fixed RR	1.25	1.04	1.00	1.52	1.37	1.13	1.00	0.79	1.36	1.05	1.19	1.25	
RRl	1.18	0.91	0.79	0.84	0.28	0.95	0.86	0.42	1.20	0.96	1.13	1.14	
RRu	1.33	1.20	1.26	2.75	6.73	1.34	1.16	1.47	1.53	1.15	1.25	1.36	
P	+++	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	+++	N.S.	+++	+++	
Between P	(*)						**			*			

	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	7	18	8	2	0	5	19	1	10	9	4	22	20	15
Het P	*	**	N.S.	N.S.		N.S.	***	N.S.	N.S.	N.S.	N.S.	***	N.S.	***
Fixed RR	1.13	1.12	1.28	1.15		1.08	1.14	1.28	1.18	1.03	1.22	1.19	1.19	1.16
RRl	1.02	1.05	1.20	0.88		0.97	1.08	1.19	1.06	0.90	1.03	1.14	1.13	1.09
RRu	1.24	1.19	1.37	1.49		1.20	1.22	1.38	1.32	1.18	1.45	1.24	1.25	1.23
P	+	+++	+++	N.S.		N.S.	+++	+++	++	N.S.	+	+++	+++	+++
Between P	*					*				N.S.			N.S.	

	Respondent for diagnosis				*Questionnaire for symptoms*			*Analysis type*		*Number of cases (lifetime asthma)*				
	medrec	parent	child	mixed	ISAAC	ATS	other	prevlnce	onset	1-50	51-100	101-200	201+	unknown
N	5	20	6	4	5	8	22	30	5	2	5	6	20	2
Het P	N.S.	***	N.S.	N.S.	N.S.	N.S.	***	***	N.S.	N.S.	N.S.	**	*	N.S.
Fixed RR	1.27	1.14	1.09	1.18	1.15	1.16	1.19	1.13	1.28	1.37	1.12	1.53	1.15	1.11
RRl	1.18	1.08	0.99	0.99	1.04	1.03	1.13	1.08	1.19	0.66	0.86	1.33	1.10	0.81
RRu	1.36	1.21	1.21	1.40	1.27	1.29	1.24	1.19	1.37	2.83	1.45	1.76	1.20	1.51
P	+++	+++	(+)	(+)	++	+	+++	+++	+++	N.S.	N.S.	+++	+++	N.S.
Between P	(*)				N.S.			**		**				

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	18	17	9	26	2	33	6	29	9	26	13	22	5	30
Het P	*	*	N.S.	***	N.S.	***	(*)	*	*	**	N.S.	***	**	**
Fixed RR	1.08	1.23	1.04	1.19	1.41	1.17	0.98	1.22	1.05	1.20	1.18	1.17	1.02	1.19
RRl	1.01	1.17	0.92	1.14	1.10	1.12	0.89	1.16	0.93	1.15	1.10	1.12	0.89	1.14
RRu	1.16	1.29	1.18	1.24	1.81	1.22	1.09	1.27	1.17	1.25	1.27	1.23	1.18	1.24
P	+	+++	N.S.	+++	++	+++	N.S.	+++	N.S.	+++	+++	+++	N.S.	+++
Between P	**		(*)		N.S.		***		*		N.S.		*	

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	3	32	3	32	4	31	12	23	1	34	14	21
Het P	N.S.	***	N.S.	***	N.S.	***	N.S.	***	N.S.	***	(*)	**
Fixed RR	1.06	1.19	1.05	1.18	1.35	1.17	1.18	1.18	1.52	1.17	1.12	1.22
RRl	0.92	1.14	0.90	1.14	1.13	1.12	1.09	1.12	0.84	1.13	1.05	1.16
RRu	1.22	1.24	1.24	1.23	1.62	1.22	1.27	1.23	2.75	1.22	1.19	1.29
P	N.S.	+++	N.S.	+++	++	+++	+++	+++	N.S.	+++	+++	+++
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		*	

	Exposed group : who is smoker		*Exposed group : when exposed*				
	Father	Father only	lif/ev	age<7y	current	unspec	other
N	33	2	10	2	9	13	1
Het P	***	N.S.	**	N.S.	*	N.S.	N.S.
Fixed RR	1.18	1.15	1.29	1.07	1.08	1.12	1.30
RRl	1.13	0.88	1.21	0.67	1.00	1.05	0.92
RRu	1.23	1.49	1.38	1.69	1.17	1.20	1.84
P	+++	N.S.	+++	N.S.	+	++	N.S.
Between P	N.S.		**				

Table C53. Continued

	Unexposed group : who is smoker			*Unexposed group : time*				*Number of adjustment variables*					
	NoHhMem	NoParent	NotSpPar	non	never	non+othr	NA	0	1	2	3-5	6-9	10+
N	2	2	31	26	9	0	0	21	4	2	3	4	1
Het P	N.S.	N.S.	***	(*)	**			*	N.S.	N.S.	N.S.	**	N.S.
Fixed RR	0.90	1.15	1.19	1.11	1.28			1.21	1.16	1.33	0.91	1.00	0.95
RRl	0.74	0.88	1.14	1.06	1.20			1.16	0.98	0.98	0.75	0.84	0.71
RRu	1.09	1.49	1.24	1.17	1.36			1.26	1.38	1.80	1.09	1.19	1.27
P	N.S.	N.S.	+++	+++	+++			+++	(+)	(+)	N.S.	N.S.	N.S.
Between P	*			**				*					

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	9	26	8	27	7	28	10	25	11	15	5	4
Het P	(*)	*	N.S.	***	*	**	*	*	(*)	**	N.S.	N.S.
Fixed RR	0.96	1.21	1.02	1.19	1.06	1.19	1.02	1.20	1.08	1.16	1.23	1.26
RRl	0.85	1.16	0.90	1.14	0.95	1.14	0.91	1.15	0.99	1.09	1.03	1.17
RRu	1.08	1.26	1.17	1.24	1.20	1.24	1.13	1.26	1.17	1.24	1.46	1.35
P	N.S.	+++	N.S.	+++	N.S.	+++	N.S.	+++	(+)	+++	+	+++
Between P	***		*		(*)		**		*			

Table C55. Children - Meta-analysis of Paternal Exposure during Lifetime, Current Asthma

This analysis is restricted to results for:
1) Current asthma
2) Paternal exposure
3) Exposure during child's lifetime (also including parent ever smoker, but not specific in utero exposure or specific discontinued exposure)
4) Results not by amount of exposure
5) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
6) WHOPAR : father regardless of mother, father only
7) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
8) UNEXSO : not father, neither parent, none in household
9) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
10) UNEXHI : not exposed defined as smoked none, or smoked none+low
11) RACE : all in study or nearest available, otherwise by race
12) For overlapping studies: principal rather than subsidiary studies, and for prospective studies, most recent follow-up

Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	24
NS	24
Wt	940.10
Het Chi	28.58
Het df	23
Het P	N.S.
Fixed RR	1.04
RRl	0.97
RRu	1.10
P	N.S.
Random RR	1.02
RRl	0.94
RRu	1.10
P	N.S.
Asymm P	N.S.

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N	24	0	0	10	2	12	0	1	9	14	0
Het P	N.S.			N.S.	N.S.	N.S.		N.S.	(*)	N.S.	
Fixed RR	1.04			1.05	1.29	1.00		0.84	0.98	1.07	
RRl	0.97			0.96	0.92	0.90		0.52	0.88	0.99	
RRu	1.10			1.14	1.80	1.10		1.36	1.09	1.16	
P	N.S.			N.S.	N.S.	N.S.		N.S.	N.S.	(+)	
Between P	N.S.			N.S.			N.S.				

Table C55. Continued

	Publication year				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	2	5	10	7	7	1	8	7	0	1
Het P	N.S.	N.S.	(*)	N.S.	N.S.	N.S.	N.S.	N.S.		N.S.
Fixed RR	1.04	0.98	1.04	1.08	0.92	1.19	1.09	0.97		1.76
RRl	0.73	0.85	0.96	0.92	0.80	0.97	0.99	0.83		0.91
RRu	1.50	1.13	1.13	1.28	1.04	1.45	1.19	1.13		3.40
P	N.S.	N.S.	N.S.	N.S.	N.S.	(+)	(+)	N.S.		(+)
Between P	N.S.				(*)					

	Country in Europe						*Country in Asia*			*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	FarEast	Cent/SE	MidlEast	0-9	10-14	15+	unknown
N	3	2	0	2	1	0	3	0	4	6	4	13	1
Het P	N.S.	N.S.		N.S.	N.S.		N.S.		N.S.	N.S.	N.S.	N.S.	N.S.
Fixed RR	0.86	1.14		0.88	1.60		0.79		1.04	1.04	1.11	0.99	0.71
RRl	0.65	1.03		0.61	0.33		0.58		0.87	0.92	0.99	0.89	0.44
RRu	1.14	1.26		1.27	7.77		1.07		1.25	1.18	1.24	1.10	1.15
P	N.S.	+		N.S.	N.S.		N.S.		N.S.	N.S.	(+)	N.S.	N.S.
Between P	N.S.						N.S.			N.S.			

	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	4	12	8	0	0	4	12	0	8	5	4	15	11	13
Het P	N.S.	N.S.	N.S.			N.S.	N.S.		N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Fixed RR	0.85	1.11	0.88			0.98	1.07		0.96	1.07	1.15	0.97	0.89	1.08
RRl	0.72	1.03	0.74			0.81	0.99		0.83	0.94	1.02	0.88	0.77	1.00
RRu	1.01	1.20	1.04			1.18	1.16		1.10	1.23	1.30	1.06	1.03	1.16
P	(-)	++	N.S.			N.S.	(+)		N.S.	N.S.	+	N.S.	N.S.	+
Between P	**					N.S.				(*)			*	

	Respondent for diagnosis				*Questionnaire for symptoms*			*Number of cases (current asthma)*				
	medrec	parent	child	mixed	ISAAC	ATS	other	1-50	51-100	101-200	201+	unknown
N	8	10	6	0	5	1	18	3	7	3	10	1
Het P	N.S.	N.S.	N.S.		N.S.	N.S.	N.S.	N.S.	N.S.	(*)	N.S.	N.S.
Fixed RR	0.88	1.08	1.04		1.10	1.41	0.96	1.17	0.90	1.06	1.05	1.60
RRl	0.75	1.00	0.89		1.01	0.80	0.88	0.78	0.74	0.81	0.98	0.33
RRu	1.03	1.16	1.21		1.21	2.48	1.06	1.76	1.10	1.40	1.13	7.77
P	N.S.	(+)	N.S.		+	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Between P	(*)				(*)			N.S.				

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	18	6	16	8	4	20	11	13	9	15	8	16	4	20
Het P	N.S.	N.S.	N.S.	N.S.	(*)	N.S.	N.S.	N.S.	(*)	N.S.	N.S.	N.S.	N.S.	N.S.
Fixed RR	1.01	1.16	1.01	1.13	0.99	1.05	1.02	1.10	1.04	1.02	1.06	1.00	0.92	1.07
RRl	0.95	0.99	0.93	1.00	0.87	0.98	0.94	0.97	0.97	0.91	0.98	0.91	0.81	1.00
RRu	1.09	1.37	1.08	1.27	1.14	1.13	1.09	1.24	1.13	1.14	1.15	1.11	1.06	1.15
P	N.S.	(+)	N.S.	(+)	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	(+)
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.		(*)	

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	5	19	6	18	4	20	5	19	4	20	11	13
Het P	*	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	(*)	N.S.
Fixed RR	1.06	1.02	1.06	1.00	0.92	1.06	0.85	1.06	1.13	0.97	1.04	1.04
RRl	0.96	0.93	0.98	0.91	0.79	0.99	0.70	0.99	1.02	0.90	0.96	0.93
RRu	1.16	1.11	1.16	1.11	1.07	1.14	1.02	1.14	1.25	1.06	1.12	1.16
P	N.S.	N.S.	N.S.	N.S.	N.S.	(+)	(-)	(+)	+	N.S.	N.S.	N.S.
Between P	N.S.		N.S.		(*)		*		*		N.S.	

	Exposed group : who is smoker		*Exposed group : when exposed*				
	Father	Father only	lif/ev	age<7y	current	unspec	other
N	22	2	7	0	6	10	1
Het P	N.S.	N.S.	N.S.		N.S.	N.S.	N.S.
Fixed RR	1.03	1.17	1.08		0.96	0.99	1.40
RRl	0.97	0.77	0.98		0.85	0.87	0.97
RRu	1.10	1.78	1.18		1.09	1.14	2.03
P	N.S.	N.S.	N.S.		N.S.	N.S.	(+)
Between P	N.S.		N.S.				

Table C55. Continued

	Unexposed group : who is smoker			*Unexposed group : time*				*Number of adjustment variables*					
	NoHhMem	NoParent	NotSpPar	non	never	non+othr	NA	0	1	2	3-5	6-9	10+
N	5	0	19	19	5	0	0	10	3	0	4	4	3
Het P	N.S.		N.S.	N.S.	N.S.			N.S.	N.S.		N.S.	N.S.	N.S.
Fixed RR	0.90		1.05	0.98	1.11			1.04	1.01		0.83	0.88	1.12
RRl	0.71		0.98	0.90	1.01			0.92	0.71		0.64	0.74	1.02
RRu	1.16		1.12	1.07	1.23			1.17	1.44		1.07	1.05	1.23
P	N.S.		N.S.	N.S.	+			N.S.	N.S.		N.S.	N.S.	+
Between P	N.S.			(*)				(*)					

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	11	13	9	15	8	16	11	13	8	7	4	5
Het P	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Fixed RR	1.04	1.03	1.04	1.03	1.07	0.99	1.03	1.05	0.97	1.06	0.92	1.09
RRl	0.96	0.92	0.95	0.94	0.98	0.90	0.96	0.93	0.85	0.91	0.74	0.99
RRu	1.12	1.16	1.13	1.14	1.16	1.09	1.11	1.17	1.10	1.23	1.14	1.20
P	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	(+)
Between P	N.S.		N.S.		N.S.		N.S.		N.S.			

Table C65. Children - Meta-analysis of Exposure during Lifetime but without Maternal Exposure, Lifetime Asthma

This analysis is restricted to results for:
1) Lifetime asthma
2) Paternal or household exposure without maternal exposure
3) Exposure during child's lifetime (also including household member ever smoker, but not specific in utero exposure or specific discontinued exposure)
4) Results not by amount of exposure
5) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
6) WHOSMO : father only, household member (but not mother)
7) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
8) UNEXSO : not specified household member, none in household
9) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
10) UNEXHI : not exposed defined as smoked none, or smoked none+low
11) RACE : all in study or nearest available, otherwise by race
12) ONSET : yes, no (prevalence)
13) For overlapping studies: principal rather than subsidiary studies

Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	10
NS	9
Wt	254.27
Het Chi	9.86
Het df	9
Het P	N.S.
Fixed RR	1.14
RRl	1.01
RRu	1.29
P	+
Random RR	1.14
RRl	1.00
RRu	1.30
P	+
Asymm P	(*)

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N	8	1	1	1	1	8	0	1	5	3	1
Het P	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.		N.S.	N.S.	N.S.	N.S.
Fixed RR	1.14	1.10	1.19	2.41	1.41	1.08		1.41	1.05	1.17	1.25
RRl	0.99	0.76	0.83	1.20	0.95	0.95		0.95	0.88	0.95	0.81
RRu	1.31	1.60	1.72	4.86	2.11	1.24		2.11	1.26	1.43	1.92
P	(+)	N.S.	N.S.	+	(+)	N.S.		(+)	N.S.	N.S.	N.S.
Between P	N.S.			*			N.S.				

Table C65. Continued

	Publication year				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	4	2	2	2	0	0	5	4	1	0
Het P	N.S.	N.S.	N.S.	N.S.			N.S.	N.S.	N.S.	
Fixed RR	1.28	0.97	1.22	1.15			1.12	1.10	1.41	
RRl	1.00	0.78	0.94	0.88			0.95	0.89	0.95	
RRu	1.64	1.22	1.57	1.49			1.32	1.35	2.11	
P	+	N.S.	N.S.	N.S.			N.S.	N.S.	(+)	
Between P	N.S.				N.S.					

	Country in Europe						*Country in Asia*			*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	FarEast	Cent/SE	MidlEast	0-9	10-14	15+	unknown
N	2	1	1	0	1	0	3	0	4	3	5	2	0
Het P	N.S.	N.S.	N.S.		N.S.		N.S.		N.S.	N.S.	N.S.	N.S.	
Fixed RR	1.50	0.86	1.07		1.20		1.17		1.10	1.52	1.05	1.15	
RRl	1.04	0.61	0.79		0.87		0.92		0.89	1.12	0.90	0.88	
RRu	2.16	1.21	1.45		1.65		1.48		1.35	2.05	1.23	1.49	
P	+	N.S.	N.S.		N.S.		N.S.		N.S.	++	N.S.	N.S.	
Between P	N.S.						N.S.			N.S.			

	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	1	4	3	2	0	0	8	0	10	3	0	7	6	4
Het P	N.S.	N.S.	N.S.	N.S.			N.S.		N.S.	N.S.		N.S.	N.S.	N.S.
Fixed RR	1.28	1.02	1.46	1.15			1.14		1.14	1.17		1.12	1.22	1.04
RRl	0.71	0.86	1.11	0.88			0.99		1.01	0.95		0.96	1.04	0.86
RRu	2.30	1.21	1.91	1.49			1.31		1.29	1.43		1.31	1.44	1.25
P	N.S.	N.S.	++	N.S.			(+)		+	N.S.		N.S.	+	N.S.
Between P	N.S.					N.S.				N.S.			N.S.	

	Respondent for diagnosis				*Questionnaire for symptoms*			*Analysis type*		*Number of cases (lifetime asthma)*				
	medrec	parent	child	mixed	ISAAC	ATS	other	prevlnce	onset	1-50	51-100	101-200	201+	unknown
N	4	6	0	0	1	4	5	9	1	0	2	2	6	0
Het P	N.S.	N.S.			N.S.	N.S.	N.S.	N.S.	N.S.		N.S.	N.S.	N.S.	
Fixed RR	1.30	1.06			1.20	1.01	1.27	1.11	1.41		1.66	1.15	1.10	
RRl	1.05	0.91			0.87	0.84	1.05	0.98	0.95		1.06	0.86	0.95	
RRu	1.60	1.24			1.65	1.21	1.54	1.27	2.11		2.61	1.54	1.26	
P	+	N.S.			N.S.	N.S.	+	N.S.	(+)		+	N.S.	N.S.	
Between P	N.S.				N.S.			N.S.		N.S.				

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	3	7	2	8	0	10	2	8	4	6	2	8	3	7
Het P	N.S.	N.S.	N.S.	N.S.		N.S.	N.S.	N.S.	*	N.S.	N.S.	N.S.	N.S.	N.S.
Fixed RR	1.11	1.15	1.03	1.18		1.14	1.03	1.18	1.18	1.11	1.28	1.10	1.11	1.15
RRl	0.91	0.99	0.81	1.03		1.01	0.81	1.03	0.97	0.95	1.00	0.95	0.91	0.99
RRu	1.36	1.35	1.30	1.37		1.29	1.30	1.37	1.43	1.30	1.64	1.26	1.36	1.35
P	N.S.	(+)	N.S.	+		+	N.S.	+	(+)	N.S.	(+)	N.S.	N.S.	(+)
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.		N.S.	

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	2	8	2	8	2	8	3	7	10	10	4	6
Het P	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Fixed RR	1.03	1.18	1.03	1.18	1.28	1.10	1.20	1.11	1.14	1.14	1.10	1.18
RRl	0.81	1.03	0.81	1.03	1.00	0.95	0.97	0.95	1.01	1.01	0.92	1.00
RRu	1.30	1.37	1.30	1.37	1.64	1.26	1.48	1.29	1.29	1.29	1.31	1.40
P	N.S.	+	N.S.	+	(+)	N.S.	(+)	N.S.	+	+	N.S.	(+)
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.	

	Exposed group : who is smoker		*Exposed group : when exposed*				
	Father only	HhNotMot	lif/ev	age<7y	current	unspec	other
N	6	4	2	1	4	3	0
Het P	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	
Fixed RR	1.11	1.20	1.37	2.41	1.11	1.03	
RRl	0.96	0.96	0.98	1.20	0.93	0.84	
RRu	1.29	1.50	1.90	4.86	1.34	1.26	
P	N.S.	N.S.	(+)	+	N.S.	N.S.	
Between P	N.S.		(*)				

Table C65. Continued

	Unexposed group : who is smoker			*Unexposed group : time*				*Number of adjustment variables*					
	NoHhMem	NoParent	NotSpPar	non	never	non+othr	NA	0	1	2	3-5	6-9	10+
N	4	2	4	8	2	0	0	6	2	0	0	1	1
Het P	N.S.	N.S.	N.S.	N.S.	N.S.			N.S.	N.S.			N.S.	N.S.
Fixed RR	1.20	1.15	1.10	1.14	1.15			1.14	1.50			0.86	1.20
RRl	0.96	0.88	0.92	0.99	0.88			0.97	1.04			0.61	0.87
RRu	1.50	1.49	1.31	1.31	1.49			1.33	2.16			1.21	1.65
P	N.S.	N.S.	N.S.	(+)	N.S.			N.S.	+			N.S.	N.S.
Between P	N.S.			N.S.				N.S.					

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	2	8	2	8	0	10	4	6	1	2	6	1
Het P	N.S.	N.S.	N.S.	N.S.		N.S.	(*)	N.S.	N.S.	N.S.	N.S.	N.S.
Fixed RR	1.03	1.18	1.03	1.18		1.14	1.15	1.14	1.20	1.02	1.22	0.86
RRl	0.81	1.03	0.81	1.03		1.01	0.94	0.97	0.87	0.72	1.04	0.61
RRu	1.30	1.37	1.30	1.37		1.29	1.39	1.33	1.65	1.44	1.43	1.21
P	N.S.	+	N.S.	+		+	N.S.	N.S.	N.S.	N.S.	+	N.S.
Between P	N.S.		N.S.		N.S.		N.S.		N.S.			

Table C67. Children - Meta-analysis of Exposure during Lifetime but without Maternal Exposure, Current Asthma

This analysis is restricted to results for:
1) Current asthma
2) Paternal or household exposure without maternal exposure
3) Exposure during child's lifetime (also including household member ever smoker, but not specific in utero exposure or specific discontinued exposure)
4) Results not by amount of exposure
5) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
6) WHOSMO : father only, household member (but not mother)
7) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
8) UNEXSO : not specified household member, none in household
9) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
10) UNEXHI : not exposed defined as smoked none, or smoked none+low
11) RACE : all in study or nearest available, otherwise by race
12) For overlapping studies: principal rather than subsidiary studies, and for prospective studies, most recent follow-up

Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	6
NS	6
Wt	211.35
Het Chi	5.52
Het df	5
Het P	N.S.
Fixed RR	1.14
RRl	1.00
RRu	1.31
P	(+)
Random RR	1.15
RRl	0.98
RRu	1.34
P	(+)
Asymm P	N.S.

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N		0	0	4	0	2	0	0	1	5	0
Het P	6			N.S.		N.S.			N.S.	N.S.	
Fixed RR	N.S.			1.14		1.17			0.56	1.16	
RRl	1.14			0.99		0.77			0.19	1.01	
RRu	1.00			1.31		1.78			1.59	1.32	
P	1.31			(+)		N.S.			N.S.	+	
Between P	(+)			N.S.			N.S.				

Table C67. Continued

	Publcation year.				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	0	1	2	3	1	0	3	1	0	1
Het P		N.S.	N.S.	N.S.	N.S.		N.S.	N.S.		N.S.
Fixed RR		0.56	1.13	1.32	1.10		1.11	1.48		1.81
RRl		0.19	0.98	0.92	0.69		0.96	0.58		0.92
RRu		1.59	1.31	1.89	1.76		1.29	3.77		3.55
P		N.S.	N.S.	N.S.	N.S.		N.S.	N.S.		(+)
Between P	N.S.				N.S.					

	Country in Europe						*Country in Asia*			*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	FarEast	Cent/SE	MidlEast	0-9	10-14	15+	unknown
N	0	2	0	1	0	0	0	0	1	3	1	2	0
Het P		N.S.		N.S.					N.S.	N.S.	N.S.	N.S.	
Fixed RR		1.13		0.56					1.48	1.31	1.04	0.98	
RRl		0.98		0.19					0.58	1.07	0.86	0.64	
RRu		1.31		1.59					3.77	1.62	1.26	1.51	
P		N.S.		N.S.					N.S.	++	N.S.	N.S.	
Between P		N.S.					N.S.			N.S.			

	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	0	3	3	0	0	0	4	0	2	2	1	3	3	3
Het P		N.S.	N.S.				N.S.		N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Fixed RR		1.13	1.33				1.14		1.17	1.23	1.04	1.33	1.33	1.13
RRl		0.98	0.82				0.99		0.77	1.00	0.86	0.82	0.82	0.98
RRu		1.30	2.16				1.31		1.78	1.50	1.26	2.16	2.16	1.30
P		(+)	N.S.				(+)		N.S.	+	N.S.	N.S.	N.S.	(+)
Between P	N.S.					N.S.				N.S.			N.S.	

	Respondent for diagnosis				*Questionnaire for symptoms*			*Number of cases (current asthma)*				
	medrec	parent	child	mixed	ISAAC	ATS	other	1-50	51-100	101-200	201+	unknown
N	2	4	0	0	2	0	4	2	1	0	3	0
Het P	(*)	N.S.			N.S.		N.S.	N.S.	N.S.		N.S.	
Fixed RR	1.28	1.13			1.13		1.21	0.96	1.81		1.13	
RRl	0.73	0.99			0.98		0.86	0.48	0.92		0.98	
RRu	2.26	1.30			1.31		1.69	1.93	3.55		1.30	
P	N.S.	(+)			N.S.		N.S.	N.S.	(+)		(+)	
Between P	N.S.				N.S.			N.S.				

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	3	3	4	2	1	5	3	3	2	4	3	3	0	6
Het P	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.		N.S.
Fixed RR	1.13	1.33	1.15	0.96	1.10	1.15	1.13	1.33	1.13	1.21	1.13	1.33		1.14
RRl	0.98	0.82	1.00	0.48	0.69	1.00	0.98	0.82	0.98	0.86	0.98	0.82		1.00
RRu	1.30	2.16	1.32	1.93	1.76	1.32	1.30	2.16	1.31	1.69	1.30	2.16		1.31
P	(+)	N.S.	+	N.S.	N.S.	(+)	(+)	N.S.	N.S.	N.S.	(+)	N.S.		(+)
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.		N.S.	

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	2	4	2	4	0	6	1	5	3	3	5	1
Het P	N.S.	N.S.	N.S.	N.S.		N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Fixed RR	1.13	1.21	1.13	1.21		1.14	1.10	1.15	1.13	1.33	1.14	1.48
RRl	0.98	0.86	0.98	0.86		1.00	0.69	1.00	0.98	0.82	0.99	0.58
RRu	1.31	1.69	1.31	1.69		1.31	1.76	1.32	1.30	2.16	1.30	3.77
P	N.S.	N.S.	N.S.	N.S.		(+)	N.S.	(+)	(+)	N.S.	(+)	N.S.
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.	

	Exposed group : who is smoker		*Exposed group : when exposed*				
	Father only	HhNotMot	lif/ev	age<7y	current	unspec	other
N	6	0	1	0	4	1	0
Het P	N.S.		N.S.		N.S.	N.S.	
Fixed RR	1.14		1.48		1.11	1.81	
RRl	1.00		0.58		0.97	0.92	
RRu	1.31		3.77		1.28	3.55	
P	(+)		N.S.		N.S.	(+)	
Between P	N.S.		N.S.				

Table C67. Continued

	Unexposed group : who is smoker			*Unexposed group : time*				*Number of adjustment variables*					
	NoHhMem	NoParent	NotSpPar	non	never	non+othr	NA	0	1	2	3-5	6-9	10+
N	2	2	2	4	2	0	0	3	0	0	0	1	2
Het P	N.S.	N.S.	(*)	N.S.	N.S.			N.S.				N.S.	N.S.
Fixed RR	1.17	1.13	1.28	1.21	1.13			1.33				1.10	1.13
RRl	0.77	0.98	0.73	0.86	0.98			0.82				0.69	0.98
RRu	1.78	1.31	2.26	1.69	1.31			2.16				1.76	1.31
P	N.S.	N.S.	N.S.	N.S.	N.S.			N.S.				N.S.	N.S.
Between P	N.S.			N.S.				N.S.					

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	3	3	3	3	2	4	3	3	3	0	3	0
Het P	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.		N.S.	
Fixed RR	1.13	1.33	1.13	1.33	1.13	1.21	1.13	1.33	1.13		1.33	
RRl	0.98	0.82	0.98	0.82	0.98	0.86	0.98	0.82	0.98		0.82	
RRu	1.30	2.16	1.30	2.16	1.31	1.69	1.30	2.16	1.30		2.16	
P	(+)	N.S.	(+)	N.S.	N.S.	N.S.	(+)	N.S.	(+)		N.S.	
Between P	N.S.		N.S.		N.S.		N.S.		N.S.			

Table C69. Children - Meta-analysis of Exposure during Lifetime but Discontinued, Household or Parent, Lifetime Asthma

This analysis is restricted to results for:
1) Lifetime asthma
2) Household (overall), or parental exposure
3) Exposure during child's lifetime but discontinued (also including parent ex smoker, but not specific in utero exposure)
4) Results not by amount of exposure
5) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
6) EXPOS : household, parent
7) WHOPAR : any/unspecified parent, mother regardless of father, mother only, father regardless of mother, father only
8) WHESMO : during child's lifetime but not current, ex (i.e. during smoker's lifetime)
9) UNEXSO : not specific parent, neither parent, none in household, none
10) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time (GILLIL: not in utero or since birth, KUHR: not since birth)
11) UNEXHI : not exposed defined as smoked none, or smoked none+low
12) RACE : all in study or nearest available, otherwise by race
13) ONSET : yes, no (prevalence)
14) For overlapping studies: principal rather than subsidiary studies

Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	7
NS	6
Wt	600.61
Het Chi	3.61
Het df	6
Het P	N.S.
Fixed RR	1.20
RRl	1.11
RRu	1.30
P	+++
Random RR	1.20
RRl	1.11
RRu	1.30
P	+++
Asymm P	N.S.

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N	5	1	1	2	1	4	0	0	2	3	2
Het P	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.			N.S.	N.S.	N.S.
Fixed RR	1.22	0.93	1.06	1.12	1.22	1.10			1.34	1.07	1.22
RRl	1.13	0.64	0.71	0.72	1.12	0.86			0.81	0.83	1.12
RRu	1.33	1.35	1.58	1.75	1.33	1.39			2.21	1.37	1.32
P	+++	N.S.	N.S.	N.S.	+++	N.S.			N.S.	N.S.	+++
Between P	N.S.			N.S.			N.S.				

Table C69. Continued

	Publication year				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	0	3	1	3	4	0	3	0	0	0
Het P		N.S.	N.S.	N.S.	N.S.		N.S.			
Fixed RR		1.20	1.49	1.20	1.09		1.22			
RRl		0.80	0.84	1.10	0.87		1.12			
RRu		1.79	2.64	1.30	1.37		1.33			
P		N.S.	N.S.	+++	N.S.		+++			
Between P	N.S.				N.S.					

	Country in Europe						*Country in Asia*			*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	FarEast	Cent/SE	MidlEast	0-9	10-14	15+	unknown
N	1	0	1	0	1	0	0	0	0	0	2	4	1
Het P	N.S.		N.S.		N.S.						N.S.	N.S.	N.S.
Fixed RR	1.22		1.61		0.97						1.22	1.10	1.24
RRl	1.12		0.64		0.49						1.12	0.86	0.69
RRu	1.33		4.06		1.92						1.32	1.39	2.25
P	+++		N.S.		N.S.						+++	N.S.	N.S.
Between P	N.S.									N.S.			

	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	2	3	2	0	0	0	3	1	3	3	1	3	6	1
Het P	N.S.	N.S.	N.S.				N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Fixed RR	1.52	0.99	1.22				1.20	1.22	1.07	1.03	1.49	1.22	1.21	0.97
RRl	0.94	0.77	1.12				0.80	1.12	0.83	0.79	0.84	1.12	1.11	0.49
RRu	2.47	1.27	1.33				1.79	1.33	1.37	1.34	2.64	1.32	1.31	1.92
P	(+)	N.S.	+++				N.S.	+++	N.S.	N.S.	N.S.	+++	+++	N.S.
Between P	N.S.					N.S.				N.S.			N.S.	

	Respondent for diagnosis				*Questionnaire for symptoms*			*Analysis type*		*Number of cases (lifetime asthma)*				
	medrec	parent	child	mixed	ISAAC	ATS	other	prevlnce	onset	1-50	51-100	101-200	201+	unknown
N	2	4	0	1	0	0	7	6	1	1	1	2	3	0
Het P	N.S.	N.S.		N.S.			N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	
Fixed RR	1.22	1.10		0.97			1.20	1.10	1.22	1.61	1.49	1.12	1.20	
RRl	1.12	0.86		0.49			1.11	0.89	1.12	0.64	0.84	0.72	1.10	
RRu	1.33	1.39		1.92			1.30	1.36	1.33	4.06	2.64	1.75	1.30	
P	+++	N.S.		N.S.			+++	N.S.	+++	N.S.	N.S.	N.S.	+++	
Between P	N.S.				N.S.			N.S.		N.S.				

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	4	3	3	4	2	5	3	4	1	6	3	4	1	6
Het P	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Fixed RR	1.10	1.22	1.07	1.22	0.99	1.22	1.03	1.22	1.24	1.20	1.07	1.22	1.49	1.20
RRl	0.86	1.12	0.83	1.12	0.75	1.13	0.79	1.12	0.69	1.11	0.83	1.12	0.84	1.10
RRu	1.39	1.32	1.37	1.33	1.30	1.33	1.34	1.33	2.25	1.30	1.37	1.33	2.64	1.30
P	N.S.	+++	N.S.	+++	N.S.	+++	N.S.	+++	N.S.	+++	N.S.	+++	N.S.	+++
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.		N.S.	

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	1	6	2	5	0	7	4	3	2	5	2	5
Het P	N.S.	N.S.	N.S.	N.S.		N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Fixed RR	1.61	1.20	1.52	1.19		1.20	1.10	1.22	0.99	1.22	0.99	1.22
RRl	0.64	1.11	0.94	1.10		1.11	0.86	1.12	0.75	1.13	0.75	1.13
RRu	4.06	1.30	2.47	1.29		1.30	1.39	1.32	1.30	1.33	1.30	1.33
P	N.S.	+++	(+)	+++		+++	N.S.	+++	N.S.	+++	N.S.	+++
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.	

	Exposed group : who is smoker				*Exposed group : when exposed*	
	AnyHh	AnyPar	Mother	Father	Ex	LifeNotC
N	2	3	2	0	4	3
Het P	N.S.	N.S.	N.S.		N.S.	N.S.
Fixed RR	0.99	1.20	1.22		1.22	1.03
RRl	0.75	0.80	1.12		1.12	0.79
RRu	1.30	1.79	1.33		1.33	1.34
P	N.S.	N.S.	+++		+++	N.S.
Between P	N.S.				N.S.	

Table C69. Continued

	Unexposed group : who is smoker			*Unexposed group : time*				*Number of adjustment variables*					
	NoHhMem	NoParent	NotSpPar	non	never	non+othr	NA	0	1	2	3-5	6-9	10+
N	2	2	3	0	4	3	0	5	0	0	0	2	0
Het P	N.S.	N.S.	N.S.		N.S.	N.S.		N.S.				N.S.	
Fixed RR	0.99	1.16	1.23		1.22	1.03		1.19				1.52	
RRl	0.75	0.67	1.13		1.12	0.79		1.10				0.94	
RRu	1.30	2.01	1.33		1.33	1.34		1.29				2.47	
P	N.S.	N.S.	+++		+++	N.S.		+++				(+)	
Between P	N.S.			N.S.				N.S.					

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	2	5	1	6	0	7	2	5	1	3	1	2
Het P	N.S.	N.S.	N.S.	N.S.		N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Fixed RR	1.52	1.19	1.49	1.20		1.20	1.52	1.19	1.22	1.03	0.97	1.52
RRl	0.94	1.10	0.84	1.10		1.11	0.94	1.10	1.12	0.80	0.49	0.94
RRu	2.47	1.29	2.64	1.30		1.30	2.47	1.29	1.33	1.32	1.92	2.47
P	(+)	+++	N.S.	+++		+++	(+)	+++	+++	N.S.	N.S.	(+)
Between P	N.S.		N.S.		N.S.		N.S.		N.S.			

Table C70. Children - Meta-analysis of Exposure during Lifetime but Discontinued, Household or Parent, Current Asthma

This analysis is restricted to results for:
1) Current asthma
2) Household (overall), or parental exposure
3) Exposure during child's lifetime but discontinued (also including parent ex smoker, but not specific in utero exposure)
4) Results not by amount of exposure
5) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
6) EXPOS : household, parent
7) WHOPAR : any/unspecified parent, mother regardless of father, mother only, father regardless of mother, father only
8) WHESMO : during child's lifetime but not current, ex (i.e. during smoker's lifetime)
9) UNEXSO : not specific parent, neither parent, none in household, none
10) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time (CUNNI1 and GILLIL: not since birth)
11) UNEXHI : not exposed defined as smoked none, or smoked none+low
12) RACE : all in study or nearest available, otherwise by race
13) For overlapping studies: principal rather than subsidiary studies, and for prospective studies, most recent follow-up
Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

Overall	
N	8
NS	8
Wt	482.67
Het Chi	12.76
Het df	7
Het P	(*)
Fixed RR	1.02
RRl	0.94
RRu	1.12
P	N.S.
Random RR	1.01
RRl	0.88
RRu	1.15
P	N.S.
Asymm P	N.S.

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N	8	0	0	2	1	5	0	1	1	6	0
Het P	(*)			*	N.S.	N.S.		N.S.	N.S.	(*)	
Fixed RR	1.02			1.10	0.87	0.97		0.87	0.93	1.08	
RRl	0.94			0.98	0.68	0.83		0.68	0.74	0.97	
RRu	1.12			1.25	1.12	1.13		1.12	1.17	1.19	
P	N.S.			N.S.	N.S.	N.S.		N.S.	N.S.	N.S.	
Between P	N.S.			N.S.			N.S.				

Table C70. Continued

	Publication year				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	0	1	4	3	4	0	4	0	0	0
Het P		N.S.	N.S.	N.S.	N.S.		*			
Fixed RR		0.87	1.07	0.98	0.97		1.06			
RRl		0.68	0.96	0.79	0.84		0.94			
RRu		1.12	1.19	1.21	1.12		1.18			
P		N.S.	N.S.	N.S.	N.S.		N.S.			
Between P	N.S.				N.S.					

	Country in Europe						*Country in Asia*			*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	FarEast	Cent/SE	MidlEast	0-9	10-14	15+	unknown
N	0	2	0	2	0	0	0	0	0	1	3	4	0
Het P		*		N.S.						N.S.	N.S.	N.S.	
Fixed RR		1.10		0.81						1.27	0.94	1.00	
RRl		0.98		0.60						1.06	0.84	0.81	
RRu		1.25		1.10						1.52	1.06	1.22	
P		N.S.		N.S.						++	N.S.	N.S.	
Between P	(*)									*			

	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	3	5	0	0	0	0	5	0	3	2	3	3	3	5
Het P	N.S.	(*)					*		N.S.	N.S.	N.S.	N.S.	N.S.	(*)
Fixed RR	0.88	1.04					1.03		1.00	1.25	0.95	0.89	0.88	1.04
RRl	0.67	0.95					0.93		0.83	1.07	0.83	0.74	0.67	0.95
RRu	1.14	1.15					1.14		1.20	1.47	1.09	1.06	1.14	1.15
P	N.S.	N.S.					N.S.		N.S.	++	N.S.	N.S.	N.S.	N.S.
Between P	N.S.					N.S.				**			N.S.	

	Respondent for diagnosis				*Questionnaire for symptoms*			*Number of cases (current asthma)*				
	medrec	parent	child	mixed	ISAAC	ATS	other	1-50	51-100	101-200	201+	unknown
N	0	6	2	0	2	1	5	0	2	1	5	0
Het P		N.S.	N.S.		*	N.S.	N.S.		N.S.	N.S.	(*)	
Fixed RR		1.05	0.81		1.10	0.87	0.97		1.05	0.70	1.04	
RRl		0.95	0.60		0.98	0.68	0.83		0.74	0.47	0.95	
RRu		1.15	1.10		1.25	1.12	1.13		1.51	1.04	1.15	
P		N.S.	N.S.		N.S.	N.S.	N.S.		N.S.	(-)	N.S.	
Between P	N.S.				N.S.			N.S.				

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	8	0	7	1	3	5	7	1	6	2	6	2	4	4
Het P	(*)		(*)	N.S.	N.S.	(*)	*	N.S.	*	N.S.	N.S.	N.S.	N.S.	(*)
Fixed RR	1.02		1.04	0.93	0.96	1.06	1.02	1.15	1.01	1.19	1.05	0.81	0.87	1.08
RRl	0.94		0.95	0.74	0.83	0.95	0.93	0.64	0.92	0.90	0.95	0.60	0.73	0.97
RRu	1.12		1.15	1.17	1.11	1.19	1.12	2.06	1.11	1.57	1.15	1.10	1.05	1.19
P	N.S.		N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Between P	N.S.		N.S.		N.S.		N.S.		N.S.		N.S.		*	

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	4	4	4	4	0	8	2	6	4	4	4	4
Het P	*	N.S.	N.S.	N.S.		(*)	N.S.	*	(*)	N.S.	(*)	N.S.
Fixed RR	1.03	1.00	1.07	0.93		1.02	1.19	1.01	1.08	0.87	1.08	0.87
RRl	0.93	0.81	0.96	0.79		0.94	0.90	0.92	0.97	0.73	0.97	0.73
RRu	1.14	1.22	1.19	1.09		1.12	1.57	1.11	1.19	1.05	1.19	1.05
P	N.S.	N.S.	N.S.	N.S.		N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Between P	N.S.		N.S.		N.S.		N.S.		*		*	

	Exposed group : who is smoker				*Exposed group : when exposed*	
	AnyHh	AnyPar	Mother	Father	Ex	LifeNotC
N	2	0	5	1	6	2
Het P	N.S.		*	N.S.	*	N.S.
Fixed RR	1.01		1.03	1.00	1.03	1.01
RRl	0.84		0.93	0.63	0.93	0.84
RRu	1.22		1.14	1.58	1.14	1.22
P	N.S.		N.S.	N.S.	N.S.	N.S.
Between P	N.S.				N.S.	

Table C70. Continued

	Unexposed group : who is smoker			*Unexposed group : time*				*Number of adjustment variables*					
	NoHhMem	NoParent	NotSpPar	non	never	non+othr	NA	0	1	2	3-5	6-9	10+
N	2	0	6	0	6	2	0	0	1	0	0	3	4
Het P	N.S.		*		*	N.S.			N.S.			N.S.	*
Fixed RR	1.01		1.03		1.03	1.01			1.15			0.98	1.03
RRl	0.84		0.93		0.93	0.84			0.64			0.79	0.93
RRu	1.22		1.14		1.14	1.22			2.06			1.21	1.14
P	N.S.		N.S.		N.S.	N.S.			N.S.			N.S.	N.S.
Between P	N.S.			N.S.				N.S.					

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	7	1	6	2	3	5	8	0	6	1	0	1
Het P	*	N.S.	*	N.S.	(*)	N.S.	(*)		*	N.S.		N.S.
Fixed RR	1.02	1.15	1.04	0.96	1.06	0.94	1.02		1.04	1.15		0.93
RRl	0.93	0.64	0.94	0.77	0.95	0.81	0.94		0.94	0.64		0.74
RRu	1.12	2.06	1.15	1.18	1.18	1.11	1.12		1.15	2.06		1.17
P	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.		N.S.	N.S.		N.S.
Between P	N.S.		N.S.		N.S.		N.S.		N.S.			

Tables D1, D2. Children - Meta-analysis of Exposure during Lifetime, Biochemical/Total (or nearest equivalent), Low/High Dose, Lifetime Asthma

These analyses are restricted to results for:
1) Lifetime asthma
2) Biochemical, total, household (overall), or parental exposure
3) Exposure during child's lifetime (also including parent ever smoker, but not specific in utero exposure or specific discontinued exposure)
4) Results for low amount of exposure (D1), or for high amount of exposure (D2)
5) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
6) EXPOS : biochemical, total, household, parent
7) BIOMEA : saliva, blood, urine
8) MEASEX : number of cigarettes, number of persons, other
9) WHOPAR : any/unspecified parent, mother regardless of father, mother only, father regardless of mother, father only
10) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
11) UNEXSO : not specific parent, neither parent, none in household, none
12) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
13) UNEXHI : not exposed defined as smoked none, or smoked none+low
14) RACE : all in study or nearest available, otherwise by race
15) ONSET : yes, no (prevalence)
16) For overlapping studies: principal rather than subsidiary studies
Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

	Table D1			Table D2		
	Low Dose			*High Dose*		
	Overall			*Overall*		
N	19			19		
NS	17			17		
Wt	857.00			349.09		
Het Chi	44.14			43.72		
Het df	18			18		
Het P	***			***		
Fixed RR	0.95			1.22		
RRl	0.89			1.10		
RRu	1.02			1.36		
P	N.S.			+++		
Random RR	1.07			1.39		
RRl	0.93			1.16		
RRu	1.22			1.68		
P	N.S.			+++		
Asymm P	*			**		
	Sex			*Sex*		
	both	male	female	both	male	female
N	15	2	2	15	2	2
Het P	***	N.S.	N.S.	**	N.S.	N.S.
Fixed RR	0.94	1.09	1.21	1.16	1.97	2.01
RRl	0.87	0.79	0.87	1.04	1.27	1.22
RRu	1.01	1.51	1.67	1.29	3.05	3.33
P	(-)	N.S.	N.S.	++	++	++
Between P	N.S.			**		
	Measure of exposure			*Measure of exposure*		
	cigs	persn	other	cigs	persn	other
N	13	3	3	13	3	3
Het P	**	N.S.	(*)	***	N.S.	N.S.
Fixed RR	0.94	0.88	1.43	1.20	1.20	1.51
RRl	0.88	0.72	1.05	1.07	0.82	1.04
RRu	1.01	1.09	1.95	1.35	1.77	2.20
P	N.S.	N.S.	+	++	N.S.	+
Between P	*			N.S.		

Tables D3, D4. Children - Meta-analysis of Exposure during Lifetime, Biochemical/Total (or nearest equivalent), Low/High Dose, Current Asthma

These analyses are restricted to results for:
1) Current asthma
2) Biochemical, total, household (overall), or parental exposure
3) Exposure during child's lifetime (also including parent ever smoker, but not specific in utero exposure or specific discontinued exposure)
4) Results for low amount of exposure (D3), or for high amount of exposure (D4)
5) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
6) EXPOS : biochemical, total, household, parent
7) BIOMEA : saliva, blood, urine
8) MEASEX : number of cigarettes, number of persons, other
9) WHOPAR : any/unspecified parent, mother regardless of father, mother only, father regardless of mother, father only
10) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
11) UNEXSO : not specific parent, neither parent, none in household, none
12) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
13) UNEXHI : not exposed defined as smoked none, or smoked none+low
14) RACE : all in study or nearest available, otherwise by race
15) For overlapping studies: principal rather than subsidiary studies, and for prospective studies, most recent follow-up
Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

	Table D3			Table D4		
	Low Dose			*High Dose*		
	Overall			*Overall*		
N	21			21		
NS	21			21		
Wt	1310.53			1377.57		
Het Chi	47.18			60.95		
Het df	20			20		
Het P	***			***		
Fixed RR	1.20			1.53		
RRl	1.14			1.45		
RRu	1.27			1.62		
P	+++			+++		
Random RR	1.08			1.40		
RRl	0.97			1.22		
RRu	1.21			1.60		
P	N.S.			+++		
Asymm P	**			N.S.		
	Sex			*Sex*		
	both	male	female	both	male	female
N	21	0	0	21	0	0
Het P	***			****		
Fixed RR	1.20			1.53		
RRl	1.14			1.45		
RRu	1.27			1.62		
P	+++			+++		
Between P	N.S.			N.S.		
	Measure of exposure			*Measure of exposure*		
	cigs	persn	other	cigs	persn	other
N	10	6	5	10	6	5
Het P	N.S.	**	(*)	N.S.	N.S.	**
Fixed RR	1.12	1.09	1.30	1.21	1.66	1.67
RRl	1.02	0.95	1.20	1.10	1.42	1.56
RRu	1.23	1.25	1.40	1.35	1.95	1.78
P	+	N.S.	+++	+++	+++	+++
Between P	*			***		

Tables D5, D6. Children - Meta-analysis of Exposure during Lifetime, Biochemical/Total (or nearest equivalent), Low/High Dose, Lifetime Asthma (or Current if Lifetime not available)

These analyses are restricted to results for:
1) Biochemical, total, household (overall), or parental exposure
2) Exposure during child's lifetime (also including parent ever smoker, but not specific in utero exposureor specific discontinued exposure)
3) Results for low amount of exposure (D5), or for high amount of exposure (D6)
4) Results complete enough for use in metaanalysis
Within each study, results are then selected (in the following order of preference, within each sex) for:
5) ASTHMA : lifetime, current
6) EXPOS : biochemical, total, household, parent
7) BIOMEA : saliva, blood, urine
8) MEASEX : number of cigarettes, number of persons, other
9) WHOPAR : any/unspecified parent, mother regardless of father, mother only, father regardless of mother, father only
10) WHESMO : during child's lifetime, ever (i.e. during smoker's lifetime), unspecified, at a specific age, current
11) UNEXSO : not specific parent, neither parent, none in household, none
12) UNEXTI : not at specified time, never (in smoker's lifetime), not at longer than specified time
13) UNEXHI : not exposed defined as smoked none, or smoked none+low
14) RACE : all in study or nearest available, otherwise by race
15) ONSET : yes, no (prevalence)
16) For overlapping studies: principal rather than subsidiary studies, and for prospective studies, most recent follow-up
Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

	Table D5			Table D6		
	Low Dose			*High Dose*		
	Overall			*Overall*		
N	36			36		
NS	34			34		
Wt	2116.46			1679.65		
Het Chi	111.42			115.94		
Het df	35			35		
Het P	***			***		
Fixed RR	1.10			1.46		
RRl	1.06			1.39		
RRu	1.15			1.53		
P	+++			+++		
Random RR	1.09			1.37		
RRl	0.99			1.22		
RRu	1.19			1.55		
P	(+)			+++		
Asymm P	N.S.			N.S.		
	Sex			*Sex*		
	both	male	female	both	male	female
N	32	2	2	32	2	2
Het P	***	N.S.	N.S.	***	N.S.	N.S.
Fixed RR	1.10	1.09	1.21	1.45	1.97	2.01
RRl	1.05	0.79	0.87	1.38	1.27	1.22
RRu	1.15	1.51	1.67	1.52	3.05	3.33
P	+++	N.S.	N.S.	+++	++	++
Between P	N.S.			N.S.		
	Measure of exposure			*Measure of exposure*		
	cigs	persn	other	cigs	persn	other
N	22	7	7	22	7	7
Het P	***	**	*	***	N.S.	*
Fixed RR	1.01	1.06	1.31	1.21	1.54	1.66
RRl	0.95	0.94	1.21	1.12	1.31	1.56
RRu	1.07	1.20	1.41	1.31	1.81	1.78
P	N.S.	N.S.	+++	+++	+++	+++
Between P	***			***		

Table E1. Children - Meta-analysis of Maternal *In Utero* Exposure (irrespective of in-life exposure), Lifetime Asthma (or Current if Lifetime not available)

This analysis is restricted to results for:
1) Exposure during gestation
2) Exposure from mother smoking
3) Results not by amount of exposure
4) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
5) ASTHMA : lifetime, current
6) UNEXSO : not specific parent, neither parent, none in household, none
7) UNEXHI : not exposed defined as smoked none, or smoked none+low
8) RACE : all in study or nearest available, otherwise by race
9) ONSET : yes, no (prevalence)
10) For overlapping studies: principal rather than subsidiary studies, and for prospective studies, most recent follow-up
Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.

See §7.10 for abbreviations and coding of p-values.

Overall	
N	32
NS	31
Wt	1283.81
Het Chi	70.34
Het df	31
Het P	***
Fixed RR	1.28
RRl	1.21
RRu	1.35
P	+++
Random RR	1.31
RRl	1.19
RRu	1.45
P	+++
Asymm P	N.S.

	Sex			*Study type*			*Start year of study*				
	both	male	female	CC	Pr	CS	<1970	1970-79	1980-89	1990+	unknown
N	30	1	1	8	6	18	0	0	9	20	3
Het P	***	N.S.	N.S.	***	*	*			N.S.	***	N.S.
Fixed RR	1.27	1.26	1.56	1.31	1.29	1.25			1.22	1.30	1.57
RRl	1.20	0.96	1.16	1.16	1.18	1.14			1.12	1.21	1.21
RRu	1.34	1.65	2.10	1.48	1.40	1.37			1.33	1.40	2.03
P	+++	(+)	++	+++	+++	+++			+++	+++	+++
Between P	N.S.			N.S.			N.S.				

	Publication year				*Continent*					
	<1990	1990-94	1995-99	2000+	NAmer	SCAmer	Europe	Asia	Auslia	Africa
N	0	3	12	17	10	1	16	2	2	1
Het P		*	**	*	N.S.	N.S.	***	N.S.	N.S.	N.S.
Fixed RR		1.04	1.24	1.31	1.41	6.90	1.27	1.21	1.05	2.20
RRl		0.81	1.12	1.23	1.24	0.80	1.18	0.92	0.88	1.28
RRu		1.33	1.37	1.41	1.59	59.76	1.35	1.59	1.26	3.78
P		N.S.	+++	+++	+++	(+)	+++	N.S.	N.S.	++
Between P	N.S	.			*					

	Country in Europe						*Highest age in RR*			
	UK	Italy	Germany	Scand	othWest	East/Bal	0-9	10-14	15+	unknown
N	3	3	2	7	0	1	15	11	6	0
Het P	N.S.	**	***	*		N.S.	***	*	N.S.	
Fixed RR	1.15	1.22	1.04	1.32		2.07	1.32	1.21	1.22	
RRl	0.96	1.07	0.69	1.21		0.85	1.23	1.07	1.08	
RRu	1.38	1.39	1.55	1.44		5.04	1.41	1.37	1.38	
P	N.S.	++	N.S.	+++		N.S.	+++	++	++	
Between P	N.S.						N.S.			

	Population setting					*Respondent for ETS exposure*				*Child smokers*			*Physician diagnosis*	
	general	school	medical	allergy	other	child	parent	med rec	mix/oth	exc/none	included	ignored	yes	no/mixed
N	11	16	4	0	1	1	23	3	5	6	2	24	16	16
Het P	N.S.	**	*		N.S.	N.S.	**	**	N.S.	N.S.	*	***	**	**
Fixed RR	1.29	1.27	1.83		1.08	6.90	1.20	1.38	1.43	1.47	1.04	1.26	1.35	1.20
RRl	1.20	1.16	1.34		0.90	0.80	1.12	1.24	1.21	1.30	0.87	1.18	1.25	1.11
RRu	1.40	1.38	2.50		1.30	59.76	1.29	1.53	1.68	1.66	1.25	1.34	1.46	1.30
P	+++	+++	+++		N.S.	(+)	+++	+++	+++	+++	N.S.	+++	+++	+++
Between P	*					*				**			*	

	Respondent for diagnosis				*Questionnaire for symptoms*			*Analysis type*		*Number of cases*				
	medrec	parent	child	mixed	ISAAC	ATS	other	prevlnce	onset	1-50	51-100	101-200	201+	unknown
N	4	22	3	3	12	0	20	28	4	1	4	12	14	1
Het P	**	**	N.S.	(*)	**		**	***	*	N.S.	N.S.	**	**	N.S.
Fixed RR	1.36	1.22	1.55	1.39	1.22		1.32	1.28	1.27	3.30	1.04	1.30	1.27	2.46
RRl	1.23	1.14	1.10	1.10	1.13		1.23	1.19	1.16	1.01	0.76	1.13	1.20	1.28
RRu	1.51	1.31	2.18	1.74	1.33		1.42	1.38	1.38	10.74	1.41	1.51	1.35	4.73
P	+++	+++	+	++	+++		+++	+++	+++	+	N.S.	+++	+++	++
Between P	N.S.				N.S.			N.S.		(*)				

	Study adjusts for or is matched on sex		*Study adjusts for or is matched on age*		*Study adjusts for or is matched on race*		*Study adjusts for or is matched on location*		*Study adjusts for or is matched on SES*		*Study adjusts for family medical history*		*Study adjusts for family composition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	24	8	13	19	9	23	11	21	14	18	20	12	8	24
Het P	***	*	***	**	N.S.	***	**	**	*	***	***	(*)	**	***
Fixed RR	1.29	1.24	1.30	1.27	1.43	1.25	1.32	1.26	1.24	1.32	1.33	1.22	1.28	1.27
RRl	1.21	1.10	1.17	1.19	1.26	1.17	1.20	1.18	1.16	1.22	1.23	1.12	1.18	1.18
RRu	1.37	1.39	1.43	1.35	1.64	1.32	1.45	1.34	1.34	1.44	1.43	1.32	1.39	1.37
P	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Between P	N.S.		N.S.		(*)		N.S.		N.S.		N.S.		N.S.	

Table E1. Continued

	Study adjusts for cooking, heating, air conditioning		*Study adjusts for housing quality, crowding, damp, mould*		*Study adjusts for pets, animal contact, farming*		*Study adjusts for child's medical history*		*Study adjusts for in utero exposure*		*Study adjusts for in life exposure*		*Asthma definition*	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Lifetime	Current
N	4	28	7	25	3	29	20	12	12	20	13	19	19	13
Het P	*	***	**	***	N.S.	***	***	*	**	**	**	**	*	***
Fixed RR	1.16	1.32	1.25	1.28	1.48	1.27	1.29	1.26	1.30	1.26	1.32	1.25	1.26	1.33
RRl	1.05	1.24	1.13	1.20	1.16	1.20	1.19	1.17	1.18	1.18	1.20	1.17	1.18	1.20
RRu	1.29	1.41	1.40	1.37	1.90	1.34	1.38	1.37	1.43	1.35	1.44	1.34	1.34	1.48
P	++	+++	+++	+++	++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Between P	*		N.S.		N.S.		N.S.		N.S.		N.S.		N.S.	

	Number of adjustment variables					
	0	1	2	3-5	6-9	10+
N	9	2	1	7	8	5
Het P	N.S.	*	N.S.	*	*	*
Fixed RR	1.27	0.96	3.30	1.51	1.23	1.23
RRl	1.13	0.68	1.01	1.32	1.12	1.10
RRu	1.43	1.35	10.74	1.73	1.34	1.39
P	+++	N.S.	+	+++	+++	+++
Between P	*					

	RR adjusted for sex		*RR adjusted for age*		*RR adjusted for other ETS*		*RR adjusted for factor other than sex, age, other ETS*		*Derivation of RR/CI*			
	Yes	No	Yes	No	Yes	No	Yes	No	Original	Numbers	SumNumbs	Other
N	17	15	9	23	12	20	21	11	18	5	1	8
Het P	**	**	**	**	**	**	***	N.S.	***	N.S.	N.S.	**
Fixed RR	1.26	1.31	1.25	1.28	1.29	1.27	1.27	1.29	1.34	1.15	1.39	1.23
RRl	1.18	1.19	1.13	1.20	1.18	1.19	1.20	1.15	1.24	0.99	0.88	1.11
RRu	1.35	1.44	1.39	1.37	1.42	1.36	1.35	1.44	1.44	1.34	2.21	1.35
P	+++	+++	+++	+++	+++	+++	+++	+++	+++	(+)	N.S.	+++
Between P	N.S.		N.S.		N.S.		N.S.		N.S.			

Tables F1, F2. Children - Meta-analysis of Maternal *In Utero* Exposure (irrespective of in-life exposure) : Low/High Dose, Current Asthma (or Lifetime if Current not available)

These analyses are restricted to results for:
1) Exposure during gestation
2) Exposure from mother smoking or ETS exposed
3) Results for low amount of exposure (F1), or for high amount of exposure (F2)
4) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
5) ASTHMA : current, lifetime
6) MEASEX : number of cigarettes, number of persons, other
7) UNEXSO : not specific parent, neither parent, none in household, none
8) UNEXHI : not exposed defined as smoked none, or smoked none+low
9) RACE : all in study or nearest available, otherwise by race
10) ONSET : yes, no (prevalence)
11) For overlapping studies: principal rather than subsidiary studies, and for prospective studies, most recent follow-up.
Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

	Table F1			Table F2		
	Low Dose			*High Dose*		
	Overall			*Overall*		
N	5			5		
NS	5			5		
Wt	276.14			186.46		
Het Chi	1.75			25.13		
Het df	4			4		
Het P	N.S.			***		
Fixed RR	1.20			1.61		
RRl	1.06			1.39		
RRu	1.35			1.86		
P	++			+++		
Random RR	1.20			2.37		
RRl	1.06			1.47		
RRu	1.35			3.81		
P	++			+++		
Asymm P	N.S.			**		
	Sex			*Sex*		
	both	male	female	both	male	female
N	5	0	0	5	0	0
Het P	N.S.			***		
Fixed RR	1.20			1.61		
RRl	1.06			1.39		
RRu	1.35			1.86		
P	++			+++		
Between P	N.S.			N.S.		
	Measure of exposure			*Measure of exposure*		
	cigs	persn	other	cigs	persn	other
N	4	1	0	4	1	0
Het P	N.S.	N.S.		***	N.S.	
Fixed RR	1.21	1.10		1.53	3.30	
RRl	1.07	0.80		1.32	1.87	
RRu	1.38	1.51		1.77	5.82	
P	++	N.S.		+++	+++	
Between P	N.S.			*		

Tables G1, G2, G3. Children - Meta-analysis of G1: *In Utero* Only Exposure, G2: In-life Only Exposure, G3: Both *In Utero* and In-life Exposure each vs No Exposure *In Utero* or In-life, Lifetime Asthma (or Current if Lifetime not available)

These analyses are restricted to results for:
1) Exposure in utero only (i.e. no in life exposure) (G1); Exposure in life only (i.e. no in utero exposure) (G2); or Exposure both in utero and in life (G3)
2) Results not by amount of exposure
3) Results complete enough for use in metaanalysis

Within each study, results are then selected (in the following order of preference, within each sex) for:
4) ASTHMA : lifetime, current
5) EXPOS : in life element of exposure/non-exposure refers to Biochemical, Household (overall), Parent (mother), Parent (father)
6) RACE : all in study or nearest available, otherwise by race
7) ONSET : yes, no (prevalence)
8) For overlapping studies: principal rather than subsidiary studies, and for prospective studies, most recent follow-up
Finally by Age: whole study if available, otherwise by widest available age group and then for single sex results (m, f) in preference to results for both sexes combined (b), and for results adjusted for the most potential confounders.
See §7.10 for abbreviations and coding of p-values.

	Table G1			Table G2			Table G3		
	Exposure in utero only			*Exposure in life only*			*Both in utero and in life*		
	Overall			*Overall*			*Overall*		
N	7			7			9		
NS	6			6			8		
Wt	85.32			496.34			459.14		
Het Chi	15.93			4.64			11.64		
Het df	6			6			8		
Het P	*			N.S.			N.S.		
Fixed RR	1.41			1.08			1.33		
RRl	1.14			0.99			1.21		
RRu	1.75			1.18			1.46		
P	++			(+)			+++		
Random RR	1.53			1.08			1.32		
RRl	1.05			0.99			1.18		
RRu	2.23			1.18			1.49		
P	+			(+)			+++		
Asymm P	N.S.			N.S.			N.S.		
	Sex			*Sex*			*Sex*		
	both	male	female	both	male	female	both	male	female
N	5	1	1	5	1	1	7	1	1
Het P	**	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Fixed RR	1.26	1.70	1.90	1.09	1.00	1.10	1.33	1.10	1.60
RRl	0.98	1.05	1.07	0.98	0.78	0.83	1.20	0.83	1.18
RRu	1.64	2.76	3.39	1.20	1.27	1.46	1.48	1.46	2.17
P	(+)	+	+	(+)	N.S.	N.S.	+++	N.S.	++
Between P	N.S.			N.S.			N.S.		

Chapter 10

INDUCTION OF ASTHMA – OVERALL ASSESSMENT

Chapter 7 describes the methods used for the assessment of the evidence on ETS exposure and asthma induction, which was carried out separately for non-smoking adults and for children. Papers published by the end of 2004 which described epidemiological studies providing relevant data were identified by extensive searches. Study details were extracted onto a study database, with RRs for a variety of definitions of outcome and exposure stored on a linked RR database, and the RRs then being used to conduct a series of meta-analyses.

The data for non-smoking adults, described in Chapter 8, consist of 17 studies providing a total of 117 RRs. An association between ETS exposure and asthma in adults is evident. Based on estimates for lifetime asthma (or if not available, for current asthma) and using exposure estimates as early in life as possible, random-effects estimates were increased for total (RR = 1.19, 95% CI = 1.04-1.35, n = 18 independent estimates), household (1.16, 1.00-1.35, n = 14), workplace (1.36, 1.09-1.70, n = 6) and childhood (1.26, 0.88-1.81, n = 4) ETS exposure. The association is little affected by restricting attention to results for never smokers, preferring RR estimates for most recent exposure or for current asthma, or using the fixed effects model. Limited data show a dose-response relationship. Although the data are consistent with ETS exposure inducing asthma in adults, they do not clearly demonstrate a cause and effect relationship. Limitations of the evidence include the relatively small number of studies (particularly those that specifically relate to induction) the lack of consideration of *in utero* exposure and the lack of control for relevant confounding variables.

The much more extensive data for children, described in Chapter 9, include 1335 RRs from a total of 227 studies. There is a clear association of in-life ETS exposure with both lifetime and current asthma, random effects meta-analysis estimates being increased for total exposure (lifetime asthma 1.23, 1.17-1.29, n = 110; current asthma 1.20, 1.13-1.27, n = 87), parental exposure (lifetime asthma 1.27, 1.21-1.33, n = 72; current asthma 1.21, 1.11-1.33, n = 45) and maternal exposure (lifetime asthma 1.31, 1.24-1.40, n = 49; current asthma 1.25, 1.12-1.40, n = 29), and more weakly for paternal exposure (lifetime asthma 1.16, 1.09-1.25, n = 35; current asthma 1.02, 0.94-1.40, n = 24). However the association is not significant where the mother does not smoke, and the exposure is only from the father (lifetime asthma 1.11, 0.96-1.29, n = 6; current asthma 1.15, 0.98-1.34) or from household members other than the mother (lifetime asthma 1.14, 1.00-1.30, n = 10; current asthma 1.15, 0.98-1.34, n = 6). There is also evidence of a dose-response relationship, with RRs typically highest for the highest exposure category considered.

Although there is considerable unexplained heterogeneity in the data, associations seen for total, parental and maternal exposure are generally consistently seen in subsets of the data defined by a wide range of factors. Exceptionally an association is not evident in studies conducted in the Far East. Associations tend to be weaker in older children, in studies where children who smoked were excluded, and in studies where the child provided data on exposure or asthma diagnosis, but the prevailing impression is of a highly consistent association.

There is no strong evidence that the association arises due to publication bias, confounding by non-smoking lifestyle factors, misclassification of exposure or diagnosis, or unreported smoking by the child.

There is, however, evidence that the association may arise wholly or in part because of uncontrolled confounding by maternal smoking in pregnancy, which shows a highly significant association with lifetime or current asthma (1.31, 1.19-1.45, n = 32) and evidence of a dose-response relationship. Among the limited number of studies that separate the individual associations with *in utero* and in-life exposure, there is a significant increase in risk associated with *in utero* only exposure (1.53, 1.05-2.23, n = 7) and with combined *in utero* and in-life exposure (1.32, 1.18-1.49, n = 9), but not with in-life only exposure (1.08, 0.99-1.18, n = 7). These results, together with the lack of clear association of risk of asthma with smoking by household members other than the mother, or in Far Eastern studies where fewer women smoke, fit in better with exposure during gestation, rather than ETS exposure in-life, being the main cause of the association of parental smoking with asthma. The increased risk of asthma seen where the mother smokes postnatally may arise because many of these mothers also smoked in pregnancy. The increased risk in some analyses associated with paternal smoking may also be due to the strong correlation between smoking by the parents.

It is also important to note that most of the studies considered in Chapters 8 and 9 do not actually provide evidence on asthma induction directly, with the number of studies that specifically relate onset of asthma to previous in-life ETS exposure being very limited.

Taking all the evidence together, we conclude that it has not been clearly demonstrated that ETS exposure can induce asthma. Although there is a clear overall tendency for the risk of asthma to be higher in ETS-exposed children and adults in the considerable number of epidemiological studies that have investigated the issue, the failure of most studies to account properly for the role of maternal smoking in pregnancy and to provide data that specifically relate asthma onset to previous in-life ETS exposure means that a causal effect of ETS exposure on asthma induction cannot be inferred with any confidence.

FINAL CONCLUSIONS

- ETS exposure can exacerbate asthma in some asthmatics.
- The available data do not allow the conclusion that ETS exposure can induce asthma in a previously non-asthmatic child or adult.

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